

Biophysical Chemistry Techniques and Nuclear Medicine Applications

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Biophysical Chemistry Applications

Biophysical chemistry

Biophysical Chemistry is a relatively new branch of chemistry that covers a broad spectrum of research activities involving biological systems. The most common feature of the research in this subject is to seek explanation of the various phenomena in biological systems in terms of either the molecules that make up the system or the supra-molecular structure of these systems.

Biophysical chemists employ various techniques used in physical chemistry to probe the structure of biological systems. These techniques include spectroscopic methods like Nuclear Magnetic Resonance (NMR) and X-ray diffraction. For example, the work for which Nobel Prize was awarded in 2009 to three chemists was based on x-ray diffraction studies of ribosomes ^[1]. Some of the areas in which biophysical chemists engage themselves are protein structure and the functional structure of cell membranes. For example, enzyme action can be explained in terms of the shape of a pocket in the protein molecule that matches the shape of the substrate molecule or its modification due to binding of a metal ion. Similarly the structure and function of the biomembranes may be understood through the study of model supramolecular structures as liposomes or phospholipid vesicles of different compositions and sizes.

The oldest reputed institute for biophysical chemistry is Max Planck Institute for Biophysical Chemistry in Göttingen.

See also

- Biophysical techniques
- Biophysics
- Biochemistry

Publications

1. Biophysical Journal
2. Archives of Biochemistry and Biophysics, Published by: Academic Press
3. Biochemical and Biophysical Research Communications, Published by: Academic Press
4. Biochimica et Biophysica Acta, Published by: Elsevier Science
5. Biophysical Chemistry, An International Journal devoted to the Physics and Chemistry of Biological Phenomena, Published by: Elsevier Science
6. Journal of Biochemical and Biophysical Methods, Published by: Elsevier Science
7. Journal of Biochemistry, Biology and Biophysics, Published by: Taylor & Francis Group
8. Journal de Chimie Physique, Physico-Chimie Biologique, International journal of physical chemistry, chemical physics and biophysics, Published by: EDP Sciences and the Societe Francaise de Chimie

References

- [1] http://nobelprize.org/nobel_prizes/chemistry/laureates/2009/press.html

DNA

Deoxyribonucleic acid ( /diˈɒksɪˈraɪboʊnuˈkleɪk ˈæsɪd/ Wikipedia:Media

helpFile:en-us-Deoxyribonucleic_acid.ogg) (**DNA**) is a nucleic acid that contains the genetic instructions used in the development and functioning of all known living organisms and some viruses. The main role of DNA molecules is the long-term storage of information. DNA is often compared to a set of blueprints or a recipe, or a code, since it contains the instructions needed to construct other components of cells, such as proteins and RNA molecules. The DNA segments that carry this genetic information are called genes, but other DNA sequences have structural purposes, or are involved in regulating the use of this genetic information.

Chemically, DNA consists of two long polymers of simple units called nucleotides, with backbones made of sugars and phosphate groups joined by ester bonds. These two strands run in opposite directions to each other and are therefore anti-parallel. Attached to each sugar is one of four types of molecules called bases. It is the sequence of these four bases along the backbone that encodes information. This information is read using the genetic code, which specifies the sequence of the amino acids within proteins. The code is read by copying stretches of DNA into the related nucleic acid RNA, in a process called transcription.

Within cells, DNA is organized into long structures called chromosomes. These chromosomes are duplicated before cells divide, in a process called DNA replication. Eukaryotic organisms (animals, plants, fungi, and protists) store most of their DNA inside the cell nucleus and some of their DNA in organelles, such as mitochondria or chloroplasts.^[1] In contrast, prokaryotes (bacteria and archaea) store their DNA only in the cytoplasm. Within the chromosomes, chromatin proteins such as histones compact and organize DNA. These compact structures guide the interactions between DNA and other proteins, helping control which parts of the DNA are transcribed.

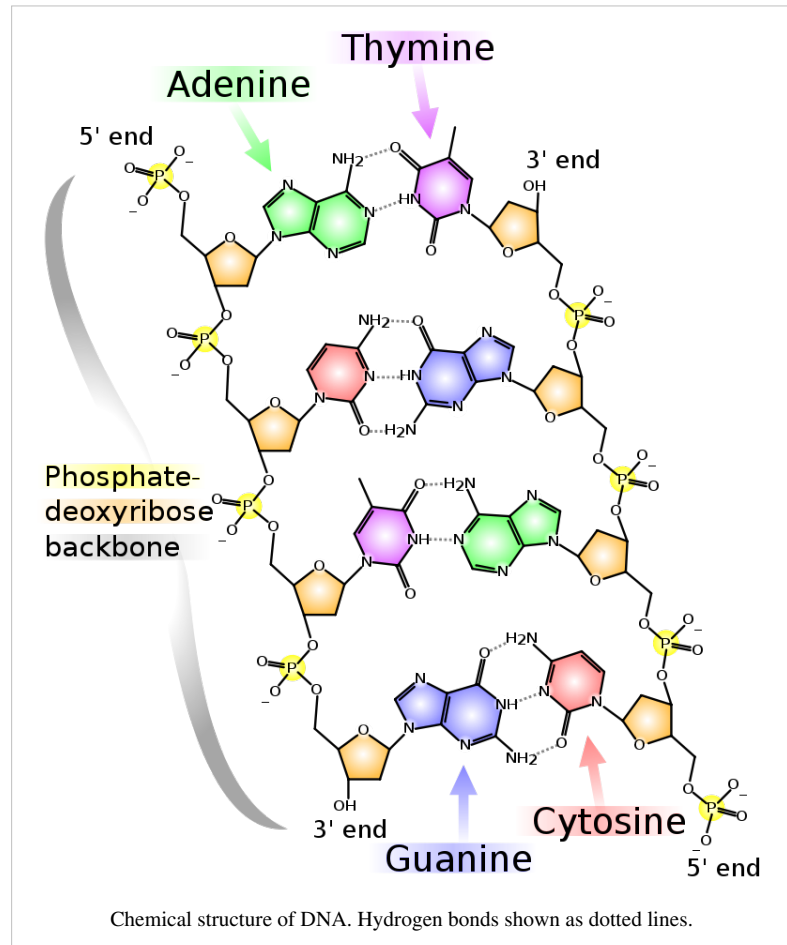
Properties

DNA is a long polymer made from repeating units called nucleotides.^{[2] [3] [4]} The DNA chain is 22 to 26 Ångströms wide (2.2 to 2.6 nanometres), and one nucleotide unit is 3.3 Å (0.33 nm) long.^[5] Although each individual repeating unit is very small, DNA polymers can be very large molecules containing millions of nucleotides. For instance, the largest human chromosome, chromosome number 1, is approximately 220 million base pairs long.^[6]

In living organisms, DNA does not usually exist as a single molecule, but instead as a pair of molecules that are held tightly together.^{[7] [8]} These two long strands entwine like vines, in the shape of a double helix. The nucleotide repeats contain both the segment of the backbone of the molecule, which holds the chain together, and a base, which interacts with the other DNA strand in the helix. A base linked to a sugar is

called a nucleoside and a base linked to a sugar and one or more phosphate groups is called a nucleotide. If multiple nucleotides are linked together, as in DNA, this polymer is called a polynucleotide.^[9]

The backbone of the DNA strand is made from alternating phosphate and sugar residues.^[10] The sugar in DNA is 2-deoxyribose, which is a pentose (five-carbon) sugar. The sugars are joined together by phosphate groups that form phosphodiester bonds between the third and fifth carbon atoms of adjacent sugar rings. These asymmetric bonds mean a strand of DNA has a direction. In a double helix the direction of the nucleotides in one strand is opposite to their direction in the other strand: the strands are *antiparallel*. The asymmetric ends of DNA strands are called the 5' (*five prime*) and 3' (*three prime*) ends, with the 5' end having a terminal phosphate group and the 3' end a terminal hydroxyl group. One major difference between DNA and RNA is the sugar, with the 2-deoxyribose in DNA being replaced by the alternative pentose sugar ribose in RNA.^[8]



The DNA double helix is stabilized by hydrogen bonds between the bases attached to the two strands. The four bases found in DNA are adenine (abbreviated A), cytosine (C), guanine (G) and thymine (T). These four bases are attached to the sugar/phosphate to form the complete nucleotide, as shown for adenosine monophosphate.

These bases are classified into two types; adenine and guanine are fused five- and six-membered heterocyclic compounds called purines, while cytosine and thymine are six-membered rings called pyrimidines.^[8] A fifth pyrimidine base, called uracil (U), usually takes the place of thymine in RNA and differs from thymine by lacking a methyl group on its ring. Uracil is not usually found in DNA, occurring only as a breakdown product of cytosine. In addition to RNA and DNA, a large number of artificial nucleic acid analogues have also been created to study the properties of nucleic acids, or for use in biotechnology.^[12]

Grooves

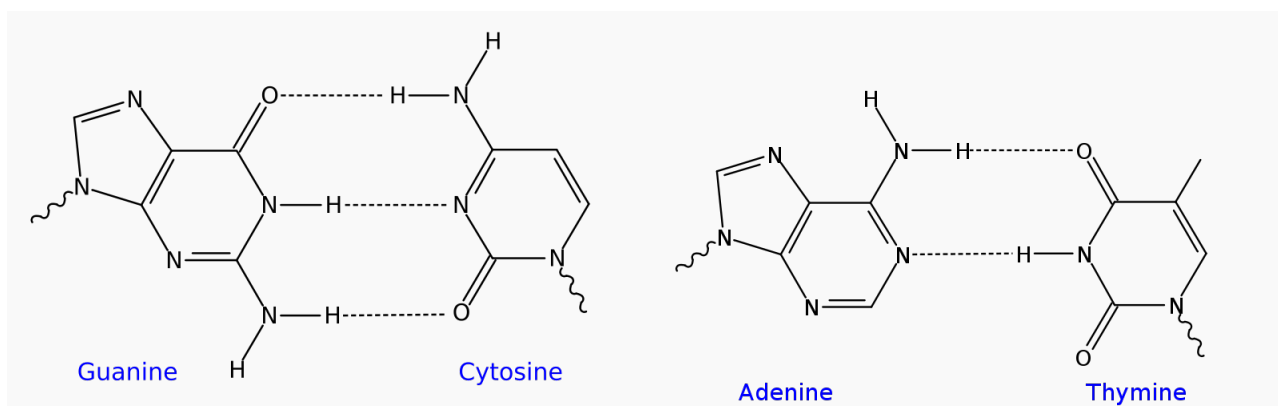
Twin helical strands form the DNA backbone. Another double helix may be found by tracing the spaces, or grooves, between the strands. These voids are adjacent to the base pairs and may provide a binding site. As the strands are not directly opposite each other, the grooves are unequally sized. One groove, the major groove, is 22 Å wide and the other, the minor groove, is 12 Å wide.^[13] The narrowness of the minor groove means that the edges of the bases are more accessible in the major groove. As a result, proteins like transcription factors that can bind to specific sequences in double-stranded DNA usually make contacts to the sides of the bases exposed in the major groove.^[14] This situation varies in unusual conformations of DNA within the cell (*see below*), but the major and minor grooves are always named to reflect the differences in size that would be seen if the DNA is twisted back into the ordinary B form.

Base pairing

Each type of base on one strand forms a bond with just one type of base on the other strand. This is called complementary base pairing. Here, purines form hydrogen bonds to pyrimidines, with A bonding only to T, and C bonding only to G. This arrangement of two nucleotides binding together across the double helix is called a base pair. As hydrogen bonds are not covalent, they can be broken and rejoined relatively easily. The two strands of DNA in a double helix can therefore be pulled apart like a zipper, either by a mechanical force or high temperature.^[15] As a result of this complementarity, all the information in the double-stranded sequence of a DNA helix is duplicated on each strand, which is vital in DNA replication. Indeed, this reversible and specific interaction between complementary base pairs is critical for all the functions of DNA in living organisms.^[3]



A section of DNA. The bases lie horizontally between the two spiraling strands.^[11] Animated version at File:DNA orbit animated.gif.



Top, a **GC** base pair with three hydrogen bonds. Bottom, an **AT** base pair with two hydrogen bonds. Non-covalent hydrogen bonds between the pairs are shown as dashed lines.

The two types of base pairs form different numbers of hydrogen bonds, AT forming two hydrogen bonds, and GC forming three hydrogen bonds (see figures, left). DNA with high GC-content is more stable than DNA with low GC-content, but contrary to popular belief, this is not due to the extra hydrogen bond of a GC base pair but rather the contribution of stacking interactions (hydrogen bonding merely provides specificity of the pairing, not stability).^[16] As a result, it is both the percentage of GC base pairs and the overall length of a DNA double helix that determine the strength of the association between the two strands of DNA. Long DNA helices with a high GC content have stronger-interacting strands, while short helices with high AT content have weaker-interacting strands.^[17] In biology, parts of the DNA double helix that need to separate easily, such as the TATAAT Pribnow box in some promoters, tend to have a high AT content, making the strands easier to pull apart.^[18] In the laboratory, the strength of this interaction can be measured by finding the temperature required to break the hydrogen bonds, their melting temperature (also called T_m value). When all the base pairs in a DNA double helix melt, the strands separate and exist in solution as two entirely independent molecules. These single-stranded DNA molecules have no single common shape, but some conformations are more stable than others.^[19]

Sense and antisense

A DNA sequence is called "sense" if its sequence is the same as that of a messenger RNA copy that is translated into protein.^[20] The sequence on the opposite strand is called the "antisense" sequence. Both sense and antisense sequences can exist on different parts of the same strand of DNA (i.e. both strands contain both sense and antisense sequences). In both prokaryotes and eukaryotes, antisense RNA sequences are produced, but the functions of these RNAs are not entirely clear.^[21] One proposal is that antisense RNAs are involved in regulating gene expression through RNA-RNA base pairing.^[22]

A few DNA sequences in prokaryotes and eukaryotes, and more in plasmids and viruses, blur the distinction between sense and antisense strands by having overlapping genes.^[23] In these cases, some DNA sequences do double duty, encoding one protein when read along one strand, and a second protein when read in the opposite direction along the other strand. In bacteria, this overlap may be involved in the regulation of gene transcription,^[24] while in viruses, overlapping genes increase the amount of information that can be encoded within the small viral genome.^[25]

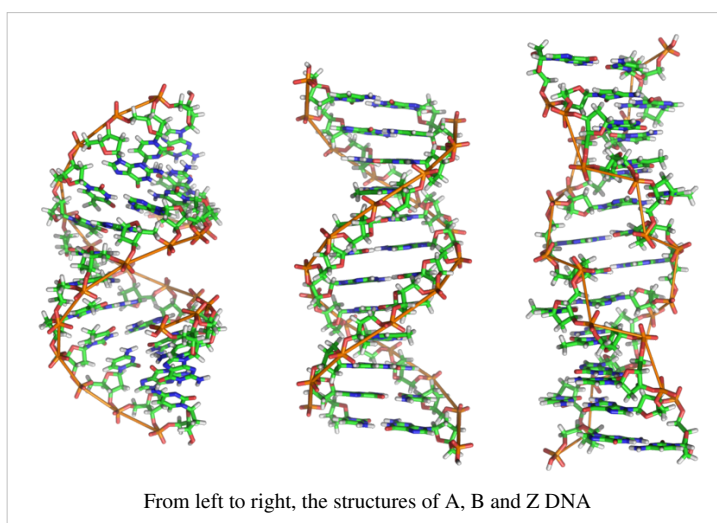
Supercoiling

DNA can be twisted like a rope in a process called DNA supercoiling. With DNA in its "relaxed" state, a strand usually circles the axis of the double helix once every 10.4 base pairs, but if the DNA is twisted the strands become more tightly or more loosely wound.^[26] If the DNA is twisted in the direction of the helix, this is positive supercoiling, and the bases are held more tightly together. If they are twisted in the opposite direction, this is negative supercoiling, and the bases come apart more easily. In nature, most DNA has slight negative supercoiling that is introduced by enzymes called topoisomerases.^[27] These enzymes are also needed to relieve the twisting

stresses introduced into DNA strands during processes such as transcription and DNA replication.^[28]

Alternate DNA structures

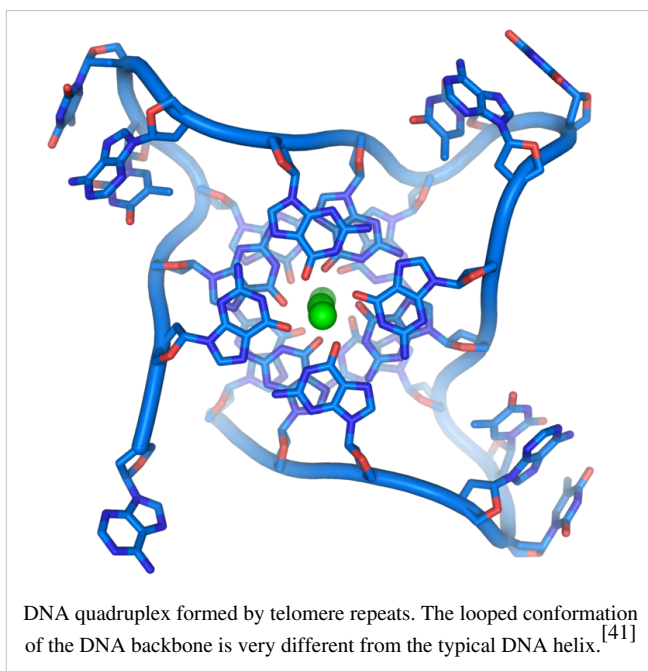
DNA exists in many possible conformations that include A-DNA, B-DNA, and Z-DNA forms, although, only B-DNA and Z-DNA have been directly observed in functional organisms.^[10] The conformation that DNA adopts depends on the hydration level, DNA sequence, the amount and direction of supercoiling, chemical modifications of the bases, the type and concentration of metal ions, as well as the presence of polyamines in solution.^[29]



The first published reports of A-DNA X-ray diffraction patterns— and also B-DNA used analyses based on Patterson transforms that provided only a limited amount of structural information for oriented fibers of DNA.^{[30] [31]} An alternate analysis was then proposed by Wilkins *et al.*, in 1953, for the *in vivo* B-DNA X-ray diffraction/scattering patterns of highly hydrated DNA fibers in terms of squares of Bessel functions.^[32] In the same journal, Watson and Crick presented their molecular modeling analysis of the DNA X-ray diffraction patterns to suggest that the structure was a double-helix.^[7]

Although the 'B-DNA form' is most common under the conditions found in cells,^[33] it is not a well-defined conformation but a family of related DNA conformations^[34] that occur at the high hydration levels present in living cells. Their corresponding X-ray diffraction and scattering patterns are characteristic of molecular paracrystals with a significant degree of disorder.^{[35] [36]}

Compared to B-DNA, the A-DNA form is a wider right-handed spiral, with a shallow, wide minor groove and a narrower, deeper major groove. The A form occurs under non-physiological conditions in partially dehydrated samples of DNA, while in the cell it may be produced in hybrid pairings of DNA and RNA strands, as well as in enzyme-DNA complexes.^{[37] [38]} Segments of DNA where the bases have been chemically modified by methylation may undergo a larger change in conformation and adopt the Z form. Here, the strands turn about the helical axis in a left-handed spiral, the opposite of the more common B form.^[39] These unusual structures can be recognized by specific Z-DNA binding proteins and may be involved in the regulation of transcription.^[40]



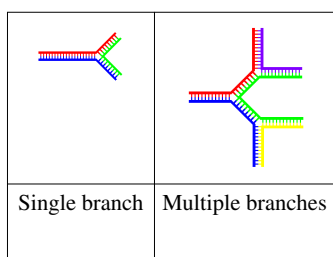
Quadruplex structures

At the ends of the linear chromosomes are specialized regions of DNA called telomeres. The main function of these regions is to allow the cell to replicate chromosome ends using the enzyme telomerase, as the enzymes that normally replicate DNA cannot copy the extreme 3' ends of chromosomes.^[42] These specialized chromosome caps also help protect the DNA ends, and stop the DNA repair systems in the cell from treating them as damage to be corrected.^[43] In human cells, telomeres are usually lengths of single-stranded DNA containing several thousand repeats of a simple TTAGGG sequence.^[44]

These guanine-rich sequences may stabilize chromosome ends by forming structures of stacked sets of four-base units, rather than the usual base

pairs found in other DNA molecules. Here, four guanine bases form a flat plate and these flat four-base units then stack on top of each other, to form a stable *G-quadruplex* structure.^[45] These structures are stabilized by hydrogen bonding between the edges of the bases and chelation of a metal ion in the centre of each four-base unit.^[46] Other structures can also be formed, with the central set of four bases coming from either a single strand folded around the bases, or several different parallel strands, each contributing one base to the central structure.

In addition to these stacked structures, telomeres also form large loop structures called telomere loops, or T-loops. Here, the single-stranded DNA curls around in a long circle stabilized by telomere-binding proteins.^[47] At the very end of the T-loop, the single-stranded telomere DNA is held onto a region of double-stranded DNA by the telomere strand disrupting the double-helical DNA and base pairing to one of the two strands. This triple-stranded structure is called a displacement loop or D-loop.^[45]

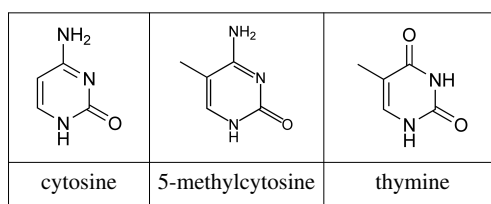


Branched DNA can form networks containing multiple branches.

Branched DNA

In DNA fraying occurs when non-complementary regions exist at the end of an otherwise complementary double-strand of DNA. However, branched DNA can occur if a third strand of DNA is introduced and contains adjoining regions able to hybridize with the frayed regions of the pre-existing double-strand. Although the simplest example of branched DNA involves only three strands of DNA, complexes involving additional strands and multiple branches are also possible.^[48] Branched DNA can be used in nanotechnology to construct geometric shapes, see the section on uses in technology below.

Chemical modifications



Structure of cytosine with and without the 5-methyl group. Deamination converts 5-methylcytosine into thymine.

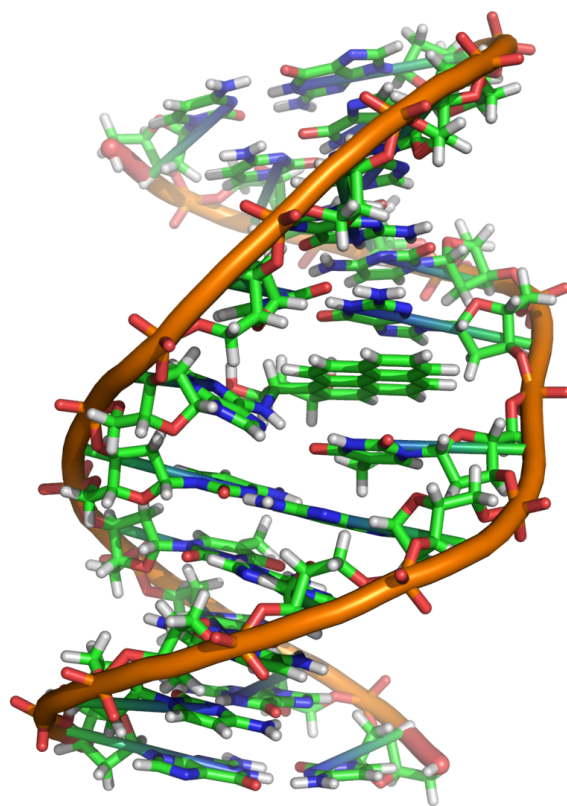
Base modifications

The expression of genes is influenced by how the DNA is packaged in chromosomes, in a structure called chromatin. Base modifications can be involved in packaging, with regions that have low or no gene expression usually containing high levels of methylation of cytosine bases. For example, cytosine methylation, produces 5-methylcytosine, which is important for X-chromosome inactivation.^[49] The average level of methylation varies between organisms - the worm *Caenorhabditis elegans* lacks cytosine methylation, while vertebrates have higher levels, with up to 1% of their DNA containing 5-methylcytosine.^[50] Despite the importance of 5-methylcytosine, it can deaminate to leave a thymine base, methylated cytosines are therefore particularly prone to mutations.^[51] Other base modifications include adenine methylation in bacteria, the presence of 5-hydroxymethylcytosine in the brain,^[52] and the glycosylation of uracil to produce the "J-base" in kinetoplasts.^[53] ^[54]

Damage

DNA can be damaged by many sorts of mutagens, which change the DNA sequence. Mutagens include oxidizing agents, alkylating agents and also high-energy electromagnetic radiation such as ultraviolet light and X-rays. The type of DNA damage produced depends on the type of mutagen. For example, UV light can damage DNA by producing thymine dimers, which are cross-links between pyrimidine bases.^[56] On the other hand, oxidants such as free radicals or hydrogen peroxide produce multiple forms of damage, including base modifications, particularly of guanosine, and double-strand breaks.^[57] A typical human cell contains about 150,000 bases that have suffered oxidative damage.^[58] Of these oxidative lesions, the most dangerous are double-strand breaks, as these are difficult to repair and can produce point mutations, insertions and deletions from the DNA sequence, as well as chromosomal translocations.^[59]

Many mutagens fit into the space between two adjacent base pairs, this is called *intercalating*. Most intercalators are aromatic and planar molecules, and include Ethidium bromide, daunomycin, and



A covalent adduct between benzo[*a*]pyrene, the major mutagen in tobacco smoke, and DNA^[55]

doxorubicin. In order for an intercalator to fit between base pairs, the bases must separate, distorting the DNA strands by unwinding of the double helix. This inhibits both transcription and DNA replication, causing toxicity and mutations. As a result, DNA intercalators are often carcinogens, and Benzo[*a*]pyrene diol epoxide, acridines, aflatoxin and ethidium bromide are well-known examples.^{[60] [61] [62]} Nevertheless, due to their ability to inhibit DNA transcription and replication, other similar toxins are also used in chemotherapy to inhibit rapidly growing cancer cells.^[63]

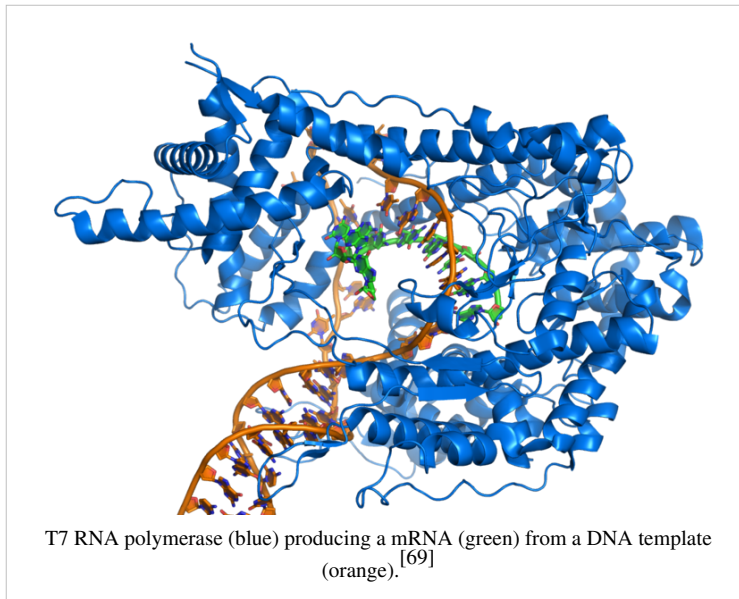
Biological functions

DNA usually occurs as linear chromosomes in eukaryotes, and circular chromosomes in prokaryotes. The set of chromosomes in a cell makes up its genome; the human genome has approximately 3 billion base pairs of DNA arranged into 46 chromosomes.^[64] The information carried by DNA is held in the sequence of pieces of DNA called genes. Transmission of genetic information in genes is achieved via complementary base pairing. For example, in transcription, when a cell uses the information in a gene, the DNA sequence is copied into a complementary RNA sequence through the attraction between the DNA and the correct RNA nucleotides. Usually, this RNA copy is then used to make a matching protein sequence in a process called translation which depends on the same interaction between RNA nucleotides. Alternatively, a cell may simply copy its genetic information in a process called DNA replication. The details of these functions are covered in other articles; here we focus on the interactions between DNA and other molecules that mediate the function of the genome.

Genes and genomes

Genomic DNA is located in the cell nucleus of eukaryotes, as well as small amounts in mitochondria and chloroplasts. In prokaryotes, the DNA is held within an irregularly shaped body in the cytoplasm called the nucleoid.^[65] The genetic information in a genome is held within genes, and the complete set of this information in an organism is called its genotype. A gene is a unit of heredity and is a region of DNA that influences a particular characteristic in an organism. Genes contain an open reading frame that can be transcribed, as well as regulatory sequences such as promoters and enhancers, which control the transcription of the open reading frame.

In many species, only a small fraction of the total sequence of the genome encodes protein. For example, only about 1.5% of the human genome consists of protein-coding exons, with over 50% of human DNA consisting of non-coding repetitive sequences.^[66] The reasons for the presence of so much non-coding DNA in eukaryotic genomes and the extraordinary differences in genome size, or *C-value*, among species represent a long-standing puzzle known as the "C-value enigma."^[67] However, DNA sequences that do not code protein may still encode functional non-coding RNA molecules, which are involved in the regulation of gene expression.^[68]



Some non-coding DNA sequences play structural roles in chromosomes. Telomeres and centromeres typically contain few genes, but are important for the function and stability of chromosomes.^{[43] [70]} An abundant form of non-coding DNA in humans are pseudogenes, which are copies of genes that have been disabled by mutation.^[71] These sequences are usually just molecular fossils, although they can occasionally serve as raw genetic material for the creation of new genes through the process of gene duplication and divergence.^[72]

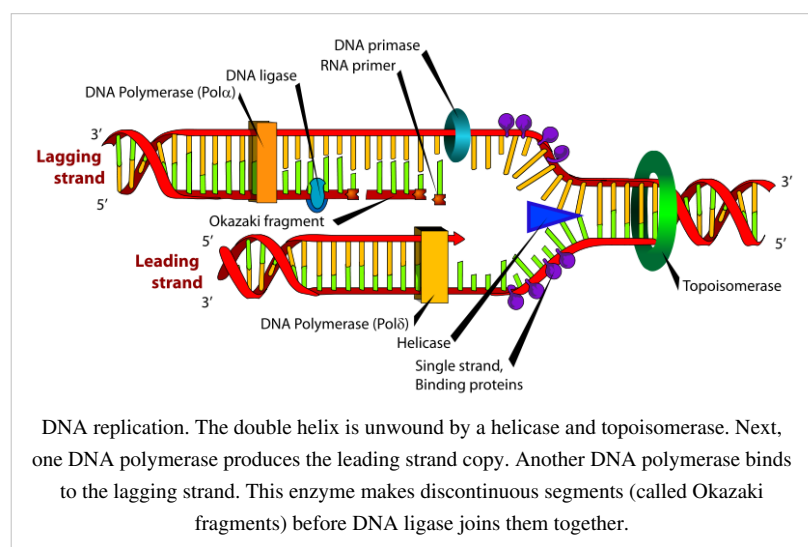
Transcription and translation

A gene is a sequence of DNA that contains genetic information and can influence the phenotype of an organism. Within a gene, the sequence of bases along a DNA strand defines a messenger RNA sequence, which then defines one or more protein sequences. The relationship between the nucleotide sequences of genes and the amino-acid sequences of proteins is determined by the rules of translation, known collectively as the genetic code. The genetic code consists of three-letter 'words' called *codons* formed from a sequence of three nucleotides (e.g. ACT, CAG, TTT).

In transcription, the codons of a gene are copied into messenger RNA by RNA polymerase. This RNA copy is then decoded by a ribosome that reads the RNA sequence by base-pairing the messenger RNA to transfer RNA, which carries amino acids. Since there are 4 bases in 3-letter combinations, there are 64 possible codons (4^3 combinations). These encode the twenty standard amino acids, giving most amino acids more than one possible codon. There are also three 'stop' or 'nonsense' codons signifying the end of the coding region; these are the TAA, TGA and TAG codons.

Replication

Cell division is essential for an organism to grow, but when a cell divides it must replicate the DNA in its genome so that the two daughter cells have the same genetic information as their parent. The double-stranded structure of DNA provides a simple mechanism for DNA replication. Here, the two strands are separated and then each strand's complementary DNA sequence is recreated by an enzyme called DNA polymerase. This enzyme makes the complementary strand by



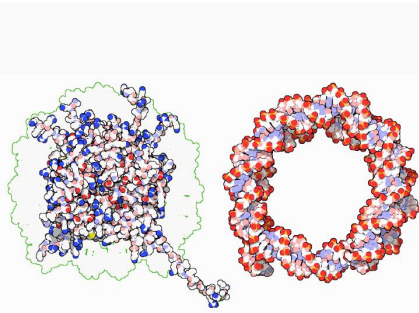
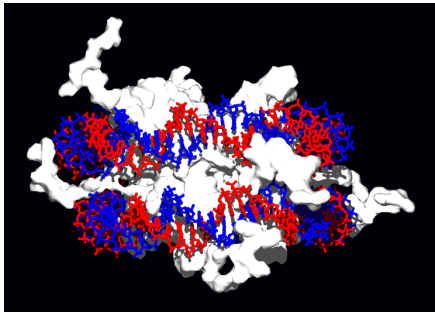
finding the correct base through complementary base pairing, and bonding it onto the original strand. As DNA polymerases can only extend a DNA strand in a 5' to 3' direction, different mechanisms are used to copy the

antiparallel strands of the double helix.^[73] In this way, the base on the old strand dictates which base appears on the new strand, and the cell ends up with a perfect copy of its DNA.

Interactions with proteins

All the functions of DNA depend on interactions with proteins. These protein interactions can be non-specific, or the protein can bind specifically to a single DNA sequence. Enzymes can also bind to DNA and of these, the polymerases that copy the DNA base sequence in transcription and DNA replication are particularly important.

DNA-binding proteins



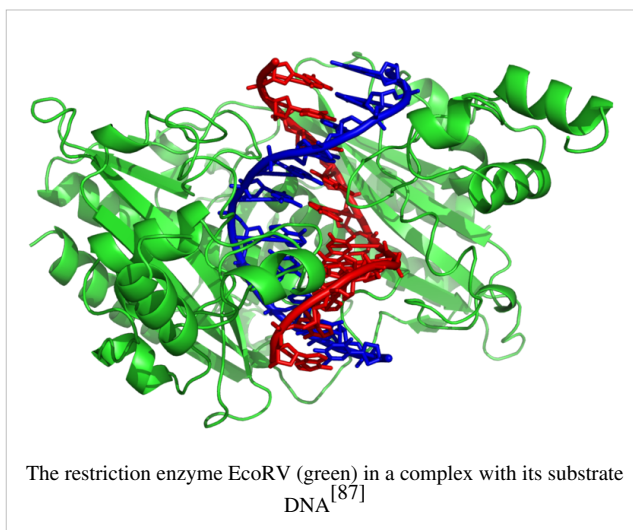
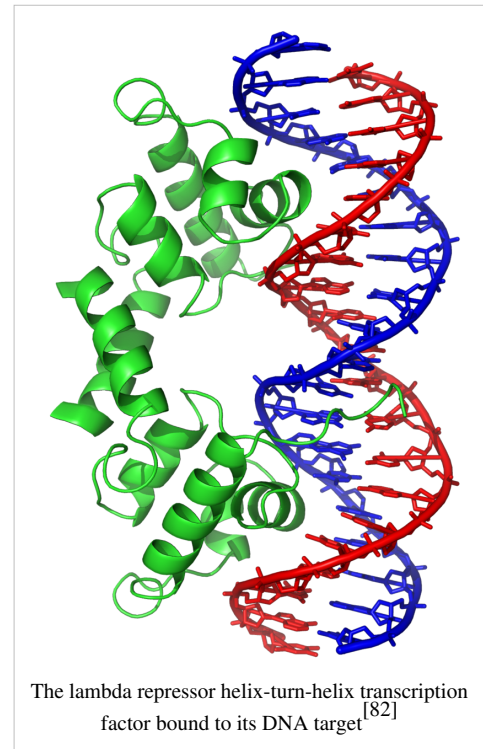
Interaction of DNA with histones (shown in white, top). These proteins' basic amino acids (below left, blue) bind to the acidic phosphate groups on DNA (below right, red).

Structural proteins that bind DNA are well-understood examples of non-specific DNA-protein interactions. Within chromosomes, DNA is held in complexes with structural proteins. These proteins organize the DNA into a compact structure called chromatin. In eukaryotes this structure involves DNA binding to a complex of small basic proteins called histones, while in prokaryotes multiple types of proteins are involved.^{[74] [75]} The histones form a disk-shaped complex called a nucleosome, which contains two complete turns of double-stranded DNA wrapped around its surface. These non-specific interactions are formed through basic residues in the histones making ionic bonds to the acidic sugar-phosphate backbone of the DNA, and are therefore largely independent of the base sequence.^[76] Chemical modifications of these basic amino acid residues include methylation, phosphorylation and acetylation.^[77] These chemical changes alter the strength of the interaction between the DNA and the histones, making the DNA more or less accessible to transcription factors and changing the rate of transcription.^[78] Other non-specific DNA-binding proteins in chromatin include the high-mobility group proteins, which bind to bent or distorted DNA.^[79] These proteins are important in bending arrays of nucleosomes and arranging them into the larger structures that make up chromosomes.^[80]

A distinct group of DNA-binding proteins are the DNA-binding proteins that specifically bind single-stranded DNA. In humans, replication protein A is the best-understood member of this family and is used in processes where the double helix is separated, including DNA replication, recombination and DNA repair.^[81] These binding proteins seem to stabilize single-stranded DNA and protect it from forming stem-loops or being degraded by nucleases.

In contrast, other proteins have evolved to bind to particular DNA sequences. The most intensively studied of these are the various transcription factors, which are proteins that regulate transcription. Each transcription factor binds to one particular set of DNA sequences and activates or inhibits the transcription of genes that have these sequences close to their promoters. The transcription factors do this in two ways. Firstly, they can bind the RNA polymerase responsible for transcription, either directly or through other mediator proteins; this locates the polymerase at the promoter and allows it to begin transcription.^[83] Alternatively, transcription factors can bind enzymes that modify the histones at the promoter; this will change the accessibility of the DNA template to the polymerase.^[84]

As these DNA targets can occur throughout an organism's genome, changes in the activity of one type of transcription factor can affect thousands of genes.^[85] Consequently, these proteins are often the targets of the signal transduction processes that control responses to environmental changes or cellular differentiation and development. The specificity of these transcription factors' interactions with DNA come from the proteins making multiple contacts to the edges of the DNA bases, allowing them to "read" the DNA sequence. Most of these base-interactions are made in the major groove, where the bases are most accessible.^[86]



DNA-modifying enzymes

Nucleases and ligases

Nucleases are enzymes that cut DNA strands by catalyzing the hydrolysis of the phosphodiester bonds. Nucleases that hydrolyse nucleotides from the ends of DNA strands are called exonucleases, while endonucleases cut within strands. The most frequently used nucleases in molecular biology are the restriction endonucleases, which cut DNA at specific sequences. For instance, the EcoRV enzyme shown to the left recognizes the 6-base sequence 5'-GAT|ATC-3' and makes a cut at the vertical line. In nature, these enzymes protect bacteria against phage infection by

digesting the phage DNA when it enters the bacterial cell, acting as part of the restriction modification system.^[88] In technology, these sequence-specific nucleases are used in molecular cloning and DNA fingerprinting.

Enzymes called DNA ligases can rejoin cut or broken DNA strands.^[89] Ligases are particularly important in lagging strand DNA replication, as they join together the short segments of DNA produced at the replication fork into a complete copy of the DNA template. They are also used in DNA repair and genetic recombination.^[89]

Topoisomerases and helicases

Topoisomerases are enzymes with both nuclease and ligase activity. These proteins change the amount of supercoiling in DNA. Some of these enzymes work by cutting the DNA helix and allowing one section to rotate, thereby reducing its level of supercoiling; the enzyme then seals the DNA break.^[27] Other types of these enzymes are capable of cutting one DNA helix and then passing a second strand of DNA through this break, before rejoining the helix.^[90] Topoisomerases are required for many processes involving DNA, such as DNA replication and transcription.^[28]

Helicases are proteins that are a type of molecular motor. They use the chemical energy in nucleoside triphosphates, predominantly ATP, to break hydrogen bonds between bases and unwind the DNA double helix into single strands.^[91] These enzymes are essential for most processes where enzymes need to access the DNA bases.

Polymerases

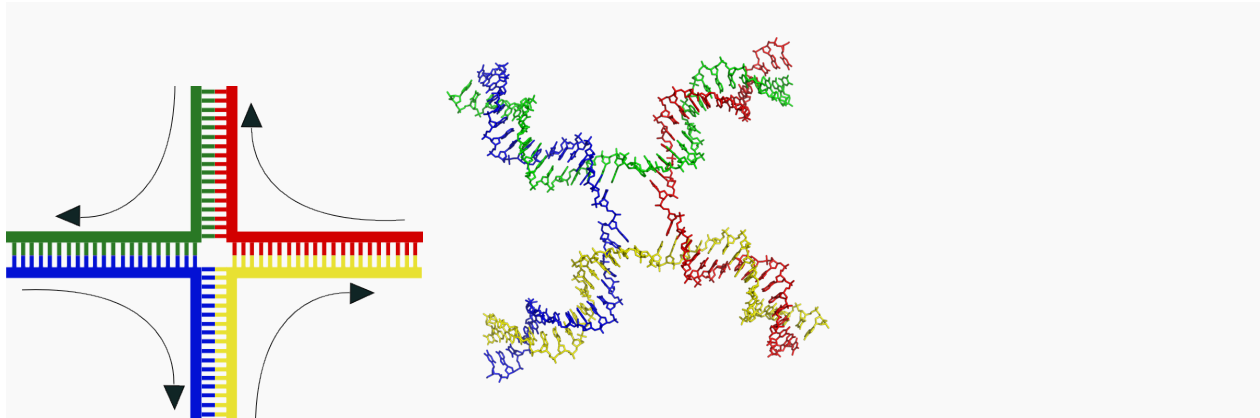
Polymerases are enzymes that synthesize polynucleotide chains from nucleoside triphosphates. The sequence of their products are copies of existing polynucleotide chains - which are called *templates*. These enzymes function by adding nucleotides onto the 3' hydroxyl group of the previous nucleotide in a DNA strand. Consequently, all polymerases work in a 5' to 3' direction.^[92] In the active site of these enzymes, the incoming nucleoside triphosphate base-pairs to the template: this allows polymerases to accurately synthesize the complementary strand of their template. Polymerases are classified according to the type of template that they use.

In DNA replication, a DNA-dependent DNA polymerase makes a copy of a DNA sequence. Accuracy is vital in this process, so many of these polymerases have a proofreading activity. Here, the polymerase recognizes the occasional mistakes in the synthesis reaction by the lack of base pairing between the mismatched nucleotides. If a mismatch is detected, a 3' to 5' exonuclease activity is activated and the incorrect base removed.^[93] In most organisms DNA polymerases function in a large complex called the replisome that contains multiple accessory subunits, such as the DNA clamp or helicases.^[94]

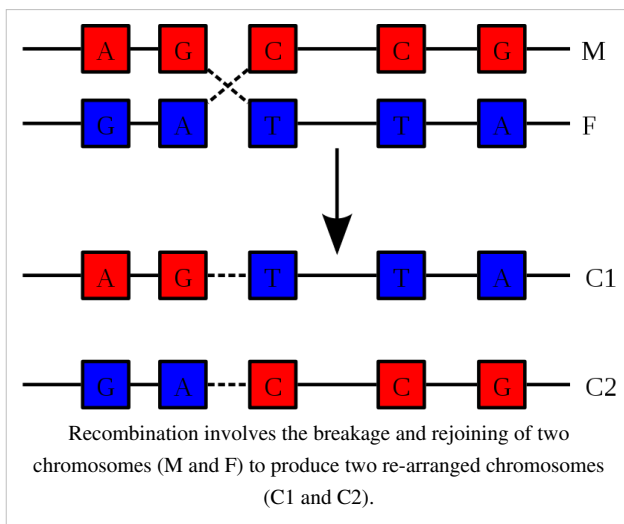
RNA-dependent DNA polymerases are a specialized class of polymerases that copy the sequence of an RNA strand into DNA. They include reverse transcriptase, which is a viral enzyme involved in the infection of cells by retroviruses, and telomerase, which is required for the replication of telomeres.^[42] ^[95] Telomerase is an unusual polymerase because it contains its own RNA template as part of its structure.^[43]

Transcription is carried out by a DNA-dependent RNA polymerase that copies the sequence of a DNA strand into RNA. To begin transcribing a gene, the RNA polymerase binds to a sequence of DNA called a promoter and separates the DNA strands. It then copies the gene sequence into a messenger RNA transcript until it reaches a region of DNA called the terminator, where it halts and detaches from the DNA. As with human DNA-dependent DNA polymerases, RNA polymerase II, the enzyme that transcribes most of the genes in the human genome, operates as part of a large protein complex with multiple regulatory and accessory subunits.^[96]

Genetic recombination



Structure of the Holliday junction intermediate in genetic recombination. The four separate DNA strands are coloured red, blue, green and yellow.^[97]



A DNA helix usually does not interact with other segments of DNA, and in human cells the different chromosomes even occupy separate areas in the nucleus called "chromosome territories".^[98] This physical separation of different chromosomes is important for the ability of DNA to function as a stable repository for information, as one of the few times chromosomes interact is during chromosomal crossover when they recombine. Chromosomal crossover is when two DNA helices break, swap a section and then rejoin.

Recombination allows chromosomes to exchange genetic information and produces new combinations of genes, which increases the efficiency of natural selection and can be important in the rapid evolution of

new proteins.^[99] Genetic recombination can also be involved in DNA repair, particularly in the cell's response to double-strand breaks.^[100]

The most common form of chromosomal crossover is homologous recombination, where the two chromosomes involved share very similar sequences. Non-homologous recombination can be damaging to cells, as it can produce chromosomal translocations and genetic abnormalities. The recombination reaction is catalyzed by enzymes known as recombinases, such as RAD51.^[101] The first step in recombination is a double-stranded break either caused by an endonuclease or damage to the DNA.^[102] A series of steps catalyzed in part by the recombinase then leads to joining of the two helices by at least one Holliday junction, in which a segment of a single strand in each helix is annealed to the complementary strand in the other helix. The Holliday junction is a tetrahedral junction structure that can be moved along the pair of chromosomes, swapping one strand for another. The recombination reaction is then halted by cleavage of the junction and re-ligation of the released DNA.^[103]

Evolution

DNA contains the genetic information that allows all modern living things to function, grow and reproduce. However, it is unclear how long in the 4-billion-year history of life DNA has performed this function, as it has been proposed that the earliest forms of life may have used RNA as their genetic material.^{[92] [104]} RNA may have acted as the central part of early cell metabolism as it can both transmit genetic information and carry out catalysis as part of ribozymes.^[105] This ancient RNA world where nucleic acid would have been used for both catalysis and genetics may have influenced the evolution of the current genetic code based on four nucleotide bases. This would occur since the number of different bases in such an organism is a trade-off between a small number of bases increasing replication accuracy and a large number of bases increasing the catalytic efficiency of ribozymes.^[106]

Unfortunately, there is no direct evidence of ancient genetic systems, as recovery of DNA from most fossils is impossible. This is because DNA will survive in the environment for less than one million years and slowly degrades into short fragments in solution.^[107] Claims for older DNA have been made, most notably a report of the isolation of a viable bacterium from a salt crystal 250 million years old,^[108] but these claims are controversial.^{[109] [110]}

Uses in technology

Genetic engineering

Methods have been developed to purify DNA from organisms, such as phenol-chloroform extraction and manipulate it in the laboratory, such as restriction digests and the polymerase chain reaction. Modern biology and biochemistry make intensive use of these techniques in recombinant DNA technology. Recombinant DNA is a man-made DNA sequence that has been assembled from other DNA sequences. They can be transformed into organisms in the form of plasmids or in the appropriate format, by using a viral vector.^[111] The genetically modified organisms produced can be used to produce products such as recombinant proteins, used in medical research,^[112] or be grown in agriculture.^{[113] [114]}

Forensics

Forensic scientists can use DNA in blood, semen, skin, saliva or hair found at a crime scene to identify a matching DNA of an individual, such as a perpetrator. This process is called genetic fingerprinting, or more accurately, DNA profiling. In DNA profiling, the lengths of variable sections of repetitive DNA, such as short tandem repeats and minisatellites, are compared between people. This method is usually an extremely reliable technique for identifying a matching DNA.^[115] However, identification can be complicated if the scene is contaminated with DNA from several people.^[116] DNA profiling was developed in 1984 by British geneticist Sir Alec Jeffreys,^[117] and first used in forensic science to convict Colin Pitchfork in the 1988 Enderby murders case.^[118]

People convicted of certain types of crimes may be required to provide a sample of DNA for a database. This has helped investigators solve old cases where only a DNA sample was obtained from the scene. DNA profiling can also be used to identify victims of mass casualty incidents.^[119] On the other hand, many convicted people have been released from prison on the basis of DNA techniques, which were not available when a crime had originally been committed.

Bioinformatics

Bioinformatics involves the manipulation, searching, and data mining of DNA sequence data. The development of techniques to store and search DNA sequences have led to widely applied advances in computer science, especially string searching algorithms, machine learning and database theory.^[120] String searching or matching algorithms, which find an occurrence of a sequence of letters inside a larger sequence of letters, were developed to search for specific sequences of nucleotides.^[121] In other applications such as text editors, even simple algorithms for this

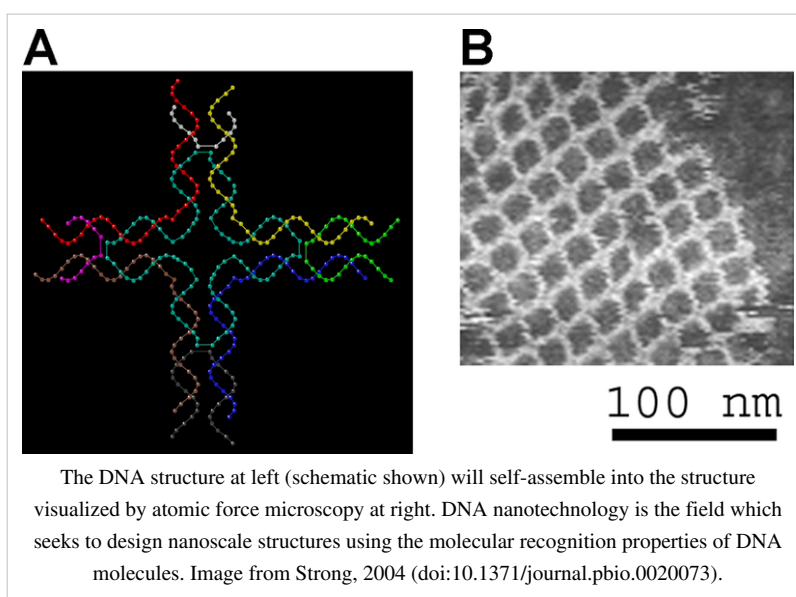
problem usually suffice, but DNA sequences cause these algorithms to exhibit near-worst-case behaviour due to their small number of distinct characters. The related problem of sequence alignment aims to identify homologous sequences and locate the specific mutations that make them distinct. These techniques, especially multiple sequence alignment, are used in studying phylogenetic relationships and protein function.^[122] Data sets representing entire genomes' worth of DNA sequences, such as those produced by the Human Genome Project, are difficult to use without annotations, which label the locations of genes and regulatory elements on each chromosome. Regions of DNA sequence that have the characteristic patterns associated with protein- or RNA-coding genes can be identified by gene finding algorithms, which allow researchers to predict the presence of particular gene products in an organism even before they have been isolated experimentally.^[123]

DNA nanotechnology

DNA nanotechnology uses the unique molecular recognition properties of DNA and other nucleic acids to create self-assembling branched DNA complexes with useful properties.^[124]

DNA is thus used as a structural material rather than as a carrier of biological information. This has led to the creation of two-dimensional periodic lattices (both tile-based as well as using the "DNA origami" method) as well as three-dimensional structures in the shapes of polyhedra.^[125] Nanomechanical devices and algorithmic self-assembly have also been demonstrated,^[126] and

these DNA structures have been used to template the arrangement of other molecules such as gold nanoparticles and streptavidin proteins.^[127]



History and anthropology

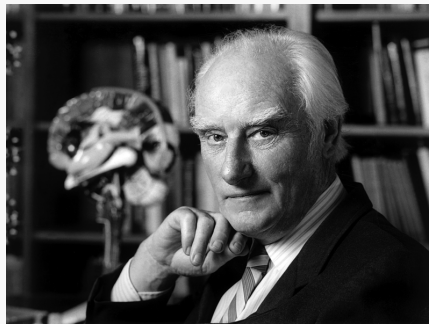
Because DNA collects mutations over time, which are then inherited, it contains historical information and by comparing DNA sequences, geneticists can infer the evolutionary history of organisms, their phylogeny.^[128] This field of phylogenetics is a powerful tool in evolutionary biology. If DNA sequences within a species are compared, population geneticists can learn the history of particular populations. This can be used in studies ranging from ecological genetics to anthropology; for example, DNA evidence is being used to try to identify the Ten Lost Tribes of Israel.^{[129] [130]}

DNA has also been used to look at modern family relationships, such as establishing family relationships between the descendants of Sally Hemings and Thomas Jefferson. This usage is closely related to the use of DNA in criminal investigations detailed above. Indeed, some criminal investigations have been solved when DNA from crime scenes has matched relatives of the guilty individual.^[131]

History of DNA research

DNA was first isolated by the Swiss physician Friedrich Miescher who, in 1869, discovered a microscopic substance in the pus of discarded surgical bandages. As it resided in the nuclei of cells, he called it "nuclein".^[132] In 1919, Phoebus Levene identified the base, sugar and phosphate nucleotide unit.^[133] Levene suggested that DNA consisted of a string of nucleotide units linked together through the phosphate groups. However, Levene thought the chain was short and the bases repeated in a fixed order. In 1937 William Astbury produced the first X-ray diffraction patterns that showed that DNA had a regular structure.^[134]

In 1928, Frederick Griffith discovered that traits of the "smooth" form of the *Pneumococcus* could be transferred to the "rough" form of the same bacteria by mixing killed "smooth" bacteria with the live "rough" form.^[135] This system provided the first clear suggestion that DNA carried genetic information—the Avery-MacLeod-McCarty experiment—when Oswald Avery, along with coworkers Colin MacLeod and Maclyn McCarty, identified DNA as the transforming principle in 1943.^[136] DNA's role in heredity was confirmed in 1952, when Alfred Hershey and Martha Chase in the Hershey-Chase experiment showed that DNA is the genetic material of the T2 phage.^[137]



Francis Crick



Rosalind Franklin



Raymond Gosling

In 1953 James D. Watson and Francis Crick suggested what is now accepted as the first correct double-helix model of DNA structure in the journal *Nature*.^[7] Their double-helix, molecular model of DNA was then based on a single X-ray diffraction image (labeled as "Photo 51")^[138] taken by Rosalind Franklin and Raymond Gosling in May 1952, as well as the information that the DNA bases were paired—also obtained through private communications from Erwin Chargaff in the previous years. Chargaff's rules played a very important role in establishing double-helix configurations for B-DNA as well as A-DNA.

Experimental evidence supporting the Watson and Crick model were published in a series of five articles in the same issue of *Nature*.^[139] Of these, Franklin and Gosling's paper was the first publication of their own X-ray diffraction data and original analysis method that partially supported the Watson and Crick model^{[31] [140]}; this issue also contained an article on DNA structure by Maurice Wilkins and two of his colleagues, whose analysis and *in vivo* B-DNA X-ray patterns also supported the presence *in vivo* of the double-helical DNA configurations as proposed by Crick and Watson for their double-helix molecular model of DNA in the previous two pages of *Nature*.^[32] In 1962, after Franklin's death, Watson, Crick, and Wilkins jointly received the Nobel Prize in Physiology or Medicine.^[141] Unfortunately, Nobel rules of the time allowed only living recipients, but a vigorous debate continues on who should receive credit for the discovery.^[142]

In an influential presentation in 1957, Crick laid out the "Central Dogma" of molecular biology, which foretold the relationship between DNA, RNA, and proteins, and articulated the "adaptor hypothesis".^[143] Final confirmation of the replication mechanism that was implied by the double-helical structure followed in 1958 through the Meselson-Stahl experiment.^[144] Further work by Crick and coworkers showed that the genetic code was based on non-overlapping triplets of bases, called codons, allowing Har Gobind Khorana, Robert W. Holley and Marshall Warren Nirenberg to decipher the genetic code.^[145] These findings represent the birth of molecular biology.

See also

- Crystallography
- DNA microarray
- DNA sequencing
- Genetic disorder
- Junk DNA
- Molecular models of DNA
- Molecular Structure of Nucleic Acids: A Structure for Deoxyribose Nucleic Acid
- Nucleic acid analogues
- Nucleic acid methods
- Nucleic acid modeling
- Nucleic Acid Notations
- Paracrystal model and theory
- X-ray crystallography
- X-ray scattering
- Phosphoramidite
- Plasmid
- Polymerase chain reaction
- *Proteopedia DNA* ^[146]
- Southern blot
- Triple-stranded DNA

Further reading

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- Olby, Robert C. (1994). *The path to the double helix: the discovery of DNA*. New York: Dover Publications. ISBN 0-486-68117-3., first published in October 1974 by MacMillan, with foreword by Francis Crick;the definitive DNA textbook, revised in 1994 with a 9 page postscript.
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- Wilkins, Maurice (2003). *The third man of the double helix the autobiography of Maurice Wilkins*. Cambridge, Eng: University Press. ISBN 0-19-860665-6.

External links

- DNA ^[147] at the Open Directory Project
- DNA binding site prediction on protein ^[148]
- DNA coiling to form chromosomes ^[149]
- DNA from the Beginning ^[150] Another DNA Learning Center site on DNA, genes, and heredity from Mendel to the human genome project.
- DNA Lab, demonstrates how to extract DNA from wheat using readily available equipment and supplies. ^[151]
- DNA the Double Helix Game ^[152] From the official Nobel Prize web site
- DNA under electron microscope ^[153]
- Dolan DNA Learning Center ^[154]
- Double Helix: 50 years of DNA ^[155], *Nature*
- Double Helix 1953–2003 ^[156] National Centre for Biotechnology Education
- Francis Crick and James Watson talking on the BBC in 1962, 1972, and 1974 ^[157]
- Genetic Education Modules for Teachers ^[158]—*DNA from the Beginning* Study Guide
- Guide to DNA cloning ^[159]
- Olby R (January 2003). "Quiet debut for the double helix" ^[160]. *Nature* **421** (6921): 402–5. doi:10.1038/nature01397. PMID 12540907.
- PDB Molecule of the Month *pdb23_1* ^[161]
- Rosalind Franklin's contributions to the study of DNA ^[162]
- The Register of Francis Crick Personal Papers 1938 - 2007 ^[163] at Mandeville Special Collections Library, Geisel Library, University of California, San Diego
- U.S. National DNA Day ^[164]—watch videos and participate in real-time chat with top scientists
- "Clue to chemistry of heredity found" ^[165]. *The New York Times*. Saturday, June 13, 1953. The first American newspaper coverage of the discovery of the DNA structure.
- An Introduction to DNA and Chromosomes ^[166] from HOPES: Huntington's Disease Outreach Project for Education at Stanford

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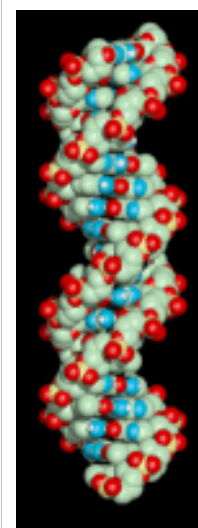
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[166] <http://hopes.stanford.edu/basics/dna/b0.html>

Molecular models of DNA

Molecular models of DNA structures are representations of the molecular geometry and topology of Deoxyribonucleic acid (DNA) molecules using one of several means, with the aim of simplifying and presenting the essential, physical and chemical, properties of DNA molecular structures either *in vivo* or *in vitro*. These representations include closely packed spheres (CPK models) made of plastic, metal wires for 'skeletal models', graphic computations and animations by computers, artistic rendering. Computer molecular models also allow animations and molecular dynamics simulations that are very important for understanding how DNA functions *in vivo*.

The more advanced, computer-based molecular models of DNA involve molecular dynamics simulations as well as quantum mechanical computations of vibro-rotations, delocalized molecular orbitals (MOs), electric dipole moments, hydrogen-bonding, and so on. **DNA molecular dynamics modeling** involves simulations of DNA molecular geometry and topology changes with time as a result of both intra- and inter- molecular interactions of DNA. Whereas molecular models of Deoxyribonucleic acid (DNA) molecules such as closely packed spheres (CPK models) made of plastic or metal wires for 'skeletal models' are useful representations of static DNA structures, their usefulness is very limited for representing complex DNA dynamics. Computer molecular modeling allows both animations and molecular dynamics simulations that are very important for understanding how DNA functions *in vivo*.



Spinning DNA
generic model.

History

Double Helix Discovery



William Astbury

Oswald Avery

Francis Crick

Erwin Chargaff

Max Delbrück

Jerry Donohue

Rosalind Franklin

Raymond Gosling

Phoebus Levene

Linus Pauling

Sir John Randall

Erwin Schrödinger

Alex Stokes

James Watson

Maurice Wilkins

Herbert Wilson

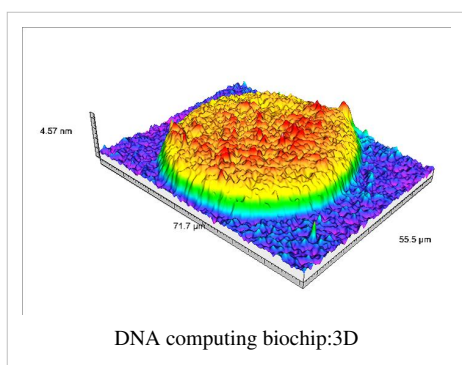
From the very early stages of structural studies of DNA by X-ray diffraction and biochemical means, molecular models such as the Watson-Crick double-helix model were successfully employed to solve the 'puzzle' of DNA structure, and also find how the latter relates to its key functions in living cells. The first high quality X-ray diffraction patterns of A-DNA were reported by Rosalind Franklin and Raymond Gosling in 1953^[1]. The first calculations of the Fourier transform of an atomic helix were reported one year earlier by Cochran, Crick and Vand^[2], and were followed in 1953 by the computation of the Fourier transform of a coiled-coil by Crick^[3].

Structural information is generated from X-ray diffraction studies of oriented DNA fibers with the help of molecular models of DNA that are combined with crystallographic and mathematical analysis of the X-ray patterns.

The first reports of a double-helix molecular model of B-DNA structure were made by Watson and Crick in 1953^[4]^[5]. Last-but-not-least, Maurice F. Wilkins, A. Stokes and H.R. Wilson, reported the first X-ray patterns of *in vivo* B-DNA in partially oriented salmon sperm heads^[6]. The development of the first correct double-helix molecular model of DNA by Crick and Watson may not have been possible without the biochemical evidence for the nucleotide base-pairing ([A---T]; [C---G]), or Chargaff's rules^{[7] [8] [9] [10] [11] [12]}. Although such initial studies of DNA structures with the help of molecular models were essentially static, their consequences for explaining the *in vivo* functions of DNA were significant in the areas of protein biosynthesis and the quasi-universality of the genetic code. Epigenetic transformation studies of DNA *in vivo* were however much slower to develop in spite of their importance for embryology, morphogenesis and cancer research. Such chemical dynamics and biochemical reactions of DNA are much more complex than the molecular dynamics of DNA physical interactions with water, ions and proteins/enzymes in living cells.

Importance

An old standing dynamic problem is how DNA "self-replication" takes place in living cells that should involve transient uncoiling of supercoiled DNA fibers. Although DNA consists of relatively rigid, very large elongated biopolymer molecules called "fibers" or chains (that are made of repeating nucleotide units of four basic types, attached to deoxyribose and phosphate groups), its molecular structure *in vivo* undergoes dynamic configuration changes that involve dynamically attached water molecules and ions. Supercoiling, packing with histones in chromosome structures, and other such supramolecular aspects also involve *in vivo* DNA topology which is even more complex than DNA molecular geometry, thus turning molecular modeling of DNA into an especially challenging problem for both molecular biologists and biotechnologists. Like other large molecules and biopolymers, DNA often exists in multiple stable geometries (that is, it exhibits conformational isomerism) and configurational, quantum states which are close to each other in energy on the potential energy surface of the DNA molecule.



Such varying molecular geometries can also be computed, at least in principle, by employing *ab initio* quantum chemistry methods that can attain high accuracy for small molecules, although claims that acceptable accuracy can be also achieved for polynucleotides, as well as DNA conformations, were recently made on the basis of VCD spectral data. Such quantum geometries define an important class of *ab initio* molecular models of DNA whose exploration has barely started especially in connection with results obtained by VCD in solutions. More detailed comparisons with such *ab initio* quantum computations are in principle obtainable through 2D-FT NMR spectroscopy and

relaxation studies of polynucleotide solutions or specifically labeled DNA, as for example with deuterium labels.

In an interesting twist of roles, the DNA molecule itself was proposed to be utilized for quantum computing. Both DNA nanostructures as well as DNA 'computing' biochips have been built (see biochip image at left).

Examples of DNA molecular models

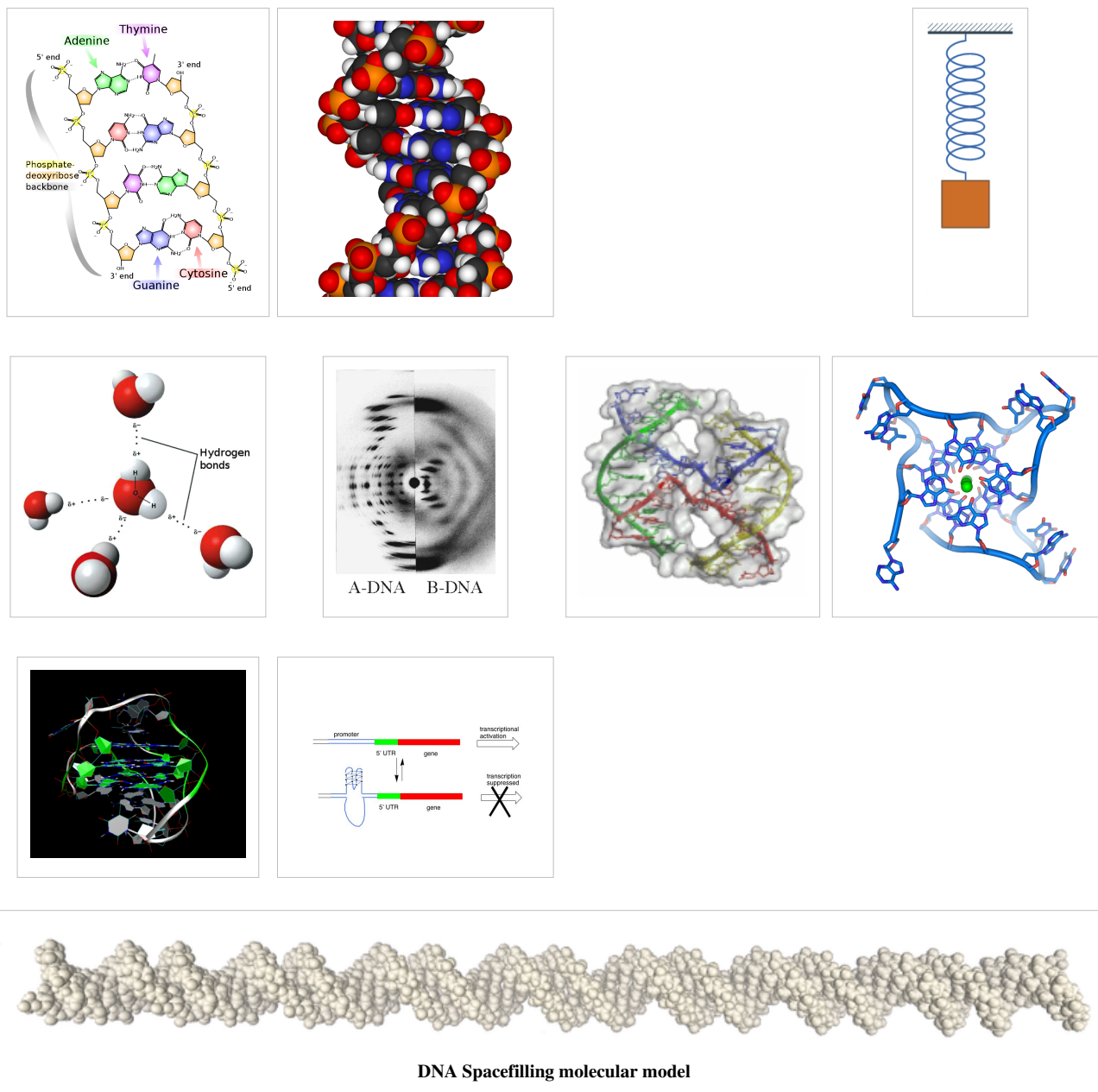
Animated molecular models allow one to visually explore the three-dimensional (3D) structure of DNA. One visualization of DNA model is a space-filling, or CPK, model. Another is a wire, or skeletal type.

The hydrogen bonding dynamics and proton exchange is very different by many orders of magnitude between the two systems of fully hydrated DNA and water molecules in ice. Thus, the DNA dynamics is complex, involving nanosecond and several tens of picosecond time scales, whereas that of liquid ice is on the picosecond time scale, and that of proton exchange in ice is on the millisecond time scale; the proton exchange rates in DNA and attached proteins may vary from picosecond to nanosecond, minutes or years, depending on the exact locations of the exchanged protons in the large biopolymers.

The chemical structure of DNA (Fig.1) is insufficient to understand the complexity of the 3D structures of DNA. On the other hand, animated molecular models allow one to visually explore the three-dimensional (3D) structure of DNA. The DNA model shown in Fig.2 of the following gallery is a space-filling, or CPK, model of the DNA double-helix, whereas the third is an animated wire, or skeletal type, molecular model of DNA (Fig.3). The last two DNA molecular models in this series depict quadruplex DNA^[13] that may be involved in certain cancers^{[14] [15]}.

A simple harmonic oscillator 'vibration' (Fig.4) is only an oversimplified dynamic representation of the longitudinal vibrations of the DNA intertwined helices which were found to be anharmonic rather than harmonic as often assumed in quantum dynamic simulations of DNA. The next figure in this gallery is a molecular model of hydrogen bonds between water molecules in ice that are similar to those found in DNA (Fig.5). Figure 6 shows the X-ray Patterns of A- and B- DNA configurations^[16] that inspired the 3D double helix molecular model of DNA. Figure 7 shows an animated 3D model of a four-way DNA junction. The last figure presents a hypothetical, G-quadruplex DNA structure that may be involved in causing cancers.

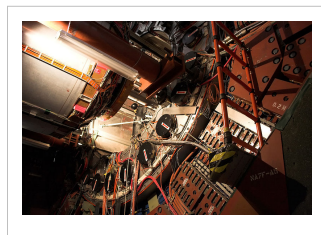
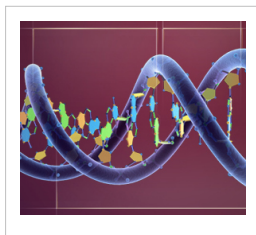
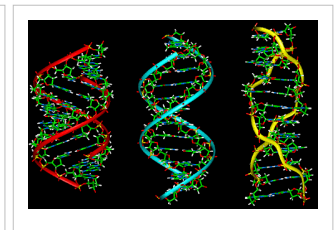
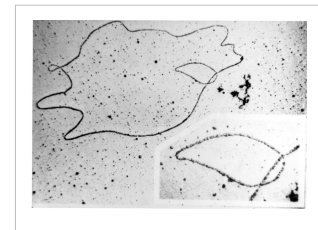
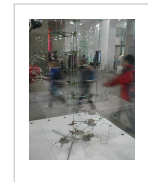
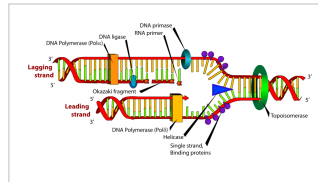
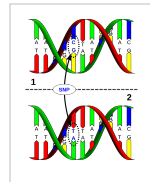
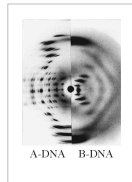
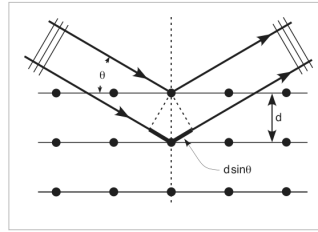
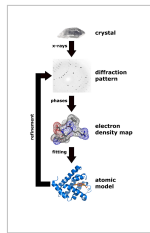
Gallery 1.



DNA structure determination using molecular modeling and X-ray patterns of DNA

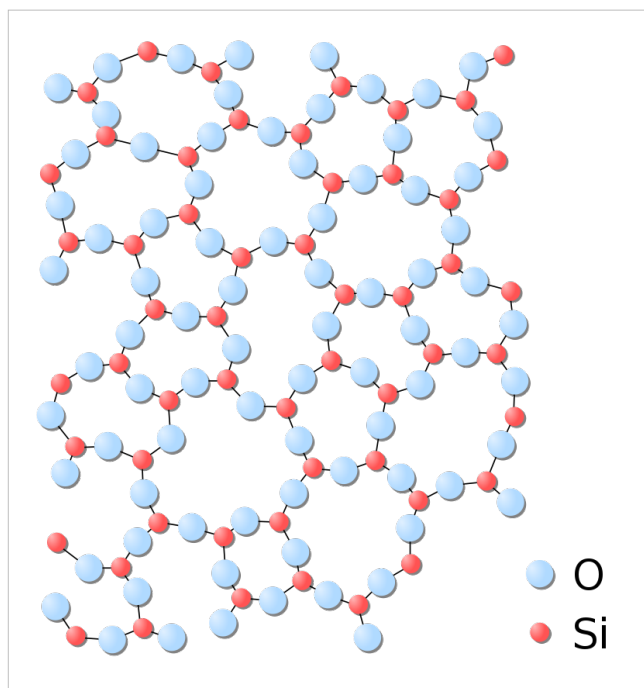
After DNA has been separated and purified by standard biochemical techniques one has a sample in a jar as shown in Fig.1 of **Gallery 2**. Figure 2 in **Gallery 2** specifies the main steps involved in generating structural information from X-ray diffraction studies of oriented DNA fibers that are drawn from the hydrated DNA sample (Fig.1) with the help of molecular models of DNA that are combined with crystallographic and mathematical analysis of the X-ray patterns. Figure 9 is an actual electron micrograph of a DNA fiber bundle, presumably of a single bacterial chromosome loop.

Gallery 2: Illustration of the molecular modeling and X-ray data collection steps involved in the determination of DNA molecular structures



Paracrystalline lattice models of B-DNA structures

A paracrystalline lattice, or paracrystal, is a molecular or atomic lattice with significant amounts (e.g., larger than a few percent) of partial disordering of molecular arrangements. Limiting cases of the paracrystal model are nanostructures, such as glasses, liquids, etc., that may possess only local ordering and no global order. A simple example of a paracrystalline lattice is shown in the following figure for a silica glass:



Liquid crystals also have paracrystalline rather than crystalline structures.

Highly hydrated B-DNA occurs naturally in living cells in such a paracrystalline state, which is a dynamic one in spite of the relatively rigid DNA double-helix stabilized by parallel hydrogen bonds between the nucleotide base-pairs in the two complementary, helical DNA chains (see figures). For simplicity most DNA molecular models omit both water and ions dynamically bound to B-DNA, and are thus less useful for understanding the dynamic behaviors of B-DNA *in vivo*. The physical and mathematical analysis of X-ray^{[17] [18]} and spectroscopic data for paracrystalline B-DNA is therefore much more complicated than that of crystalline, A-DNA X-ray diffraction patterns. The paracrystal model is also important for DNA technological applications such as DNA nanotechnology. Novel techniques that combine X-ray diffraction of DNA with X-ray microscopy in hydrated living cells are now also being developed (see, for example, "Application of X-ray microscopy in the analysis of living hydrated cells"^[19]).

Genomic and biotechnology applications of DNA molecular modeling

There are various uses of DNA molecular modeling in Genomics and Biotechnology research applications, from DNA repair to PCR and DNA nanostructures. Two-dimensional DNA junction arrays have been visualized by Atomic force microscopy.^[20]

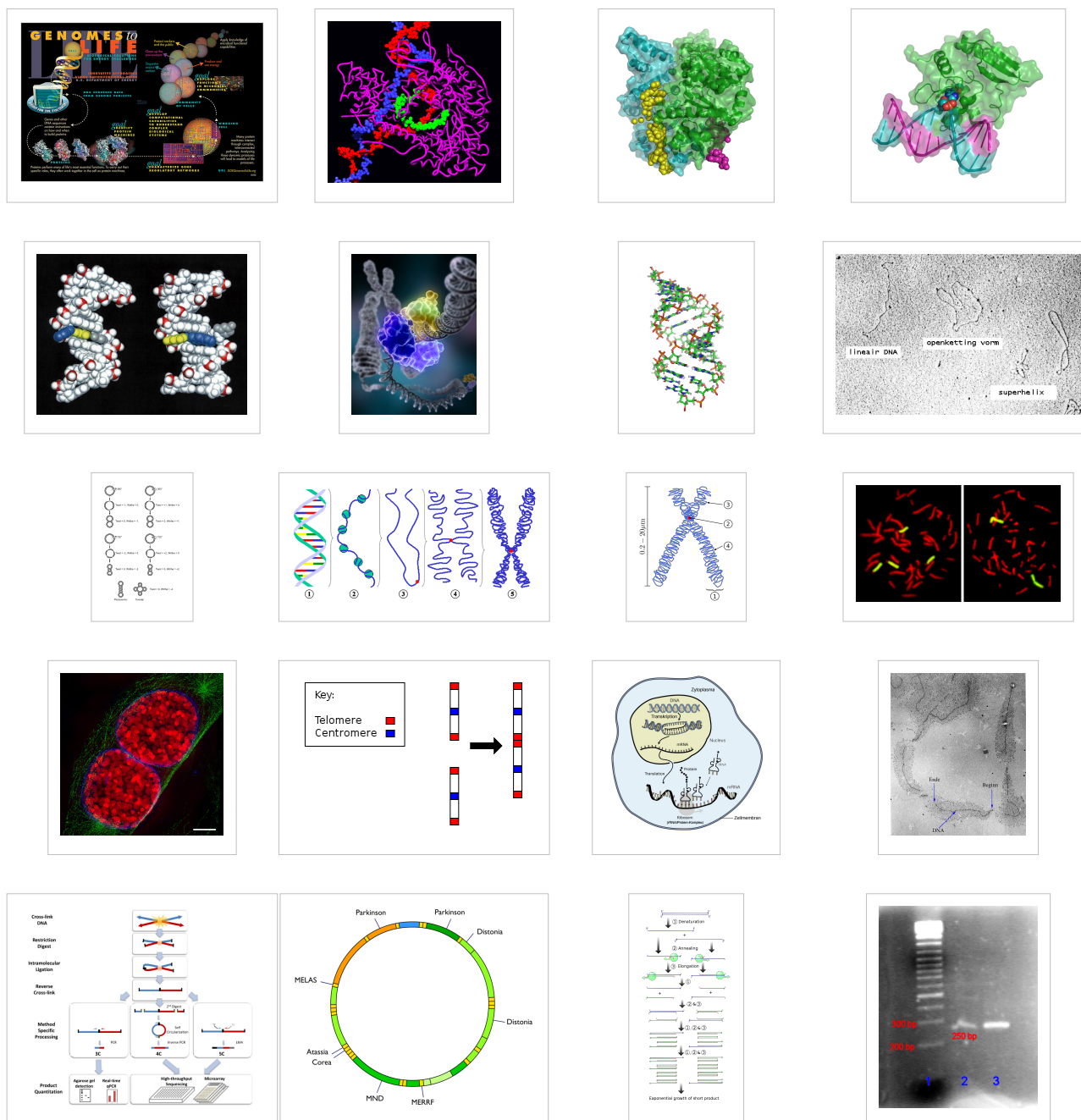
The following **Gallery 3** consists of images that illustrate various uses of DNA molecular modeling in Genomics and Biotechnology research applications from DNA repair to PCR and DNA nanostructures; each slide contains its own explanation and/or details. The first slide presents an overview of DNA applications, including DNA molecular models, with emphasis on Genomics and Biotechnology.

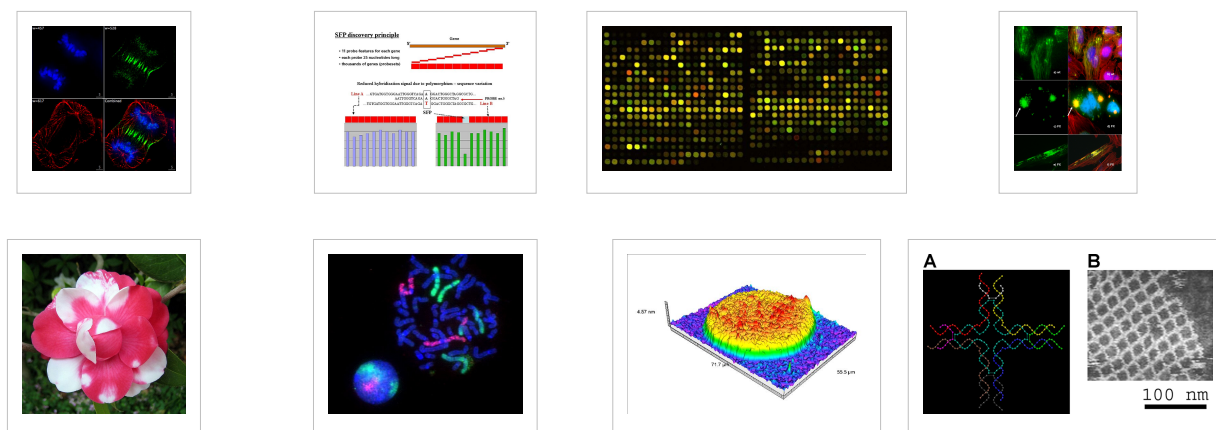
- The *first row*: Fig.2 shows a computer molecular model of RNA polymerase, followed in Figure 3 by that of an *E. coli*, bacterial DNA primase template suggesting very complex dynamics at the interfaces between the enzymes

and the DNA template; the next Figures 4 and 5 illustrate in computed molecular models the mutagenic, chemical interaction of potent carcinogen molecules with DNA.

- The *last row* figures in **Gallery 3** present a DNA biochip and DNA nanostructures designed for DNA computing and other dynamic applications of DNA nanotechnology; last image in this row is of self-assembled DNA nanostructures. The DNA “tile” structure in this image consists of four branched junctions oriented at 90° angles. Each tile consists of nine DNA oligonucleotides as shown; such tiles serve as the primary “building block” for the assembly of the DNA nanogrids shown in the AFM micrograph.

Gallery 3: DNA molecular modeling applications in Genomics and Biotechnology





Quadruplex DNA ^[13] may be involved in certain cancers ^{[21] [22]} ; see also Figures 8 to 10 above in **Gallery 1**.

See also

DNA biochemistry

- DNA
- DNA structure
- G-quadruplex

X-ray and neutron crystallography

- Crystallography
- Crystal lattices
- X-ray scattering
- Sir Lawrence Bragg, FRS
- List of nucleic acid simulation software
- Neutron scattering
- X-ray microscopy
- Sirius visualization software
- QMC@Home

Spectroscopy

- 2D-FT NMRI and Spectroscopy
- FT-NMR ^{[23] [24]}
 - NMR Atlas--database ^[25]
 - mmCIF downloadable coordinate files of nucleic acids in solution from 2D-FT NMR data ^[26]
 - NMR constraints files for NAs in PDB format ^[27]
- NMR microscopy ^[28]
- Microwave spectroscopy
- Vibrational circular dichroism (VCD)
- FT-IR
- FT-NIR ^{[29] [30] [31]}
- Spectral, Hyperspectral, and Chemical imaging ^{[32] [33] [34] [29] [30] [35] [36]} .
- Raman spectroscopy/microscopy ^[37] and CARS ^[38] .

- Fluorescence correlation spectroscopy^{[39] [40] [41] [30] [42] [43] [44] [29]}, Fluorescence cross-correlation spectroscopy and FRET^{[45] [46] [47]}.
- Confocal microscopy^[39]

Further reading

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External links

- DNA the Double Helix Game ^[152] From the official Nobel Prize web site
- MDDNA: Structural Bioinformatics of DNA ^[50]
- Double Helix 1953–2003 ^[156] National Centre for Biotechnology Education
- DNALive: a web interface to compute DNA physical properties ^[51]. Also allows cross-linking of the results with the UCSC Genome browser and DNA dynamics.
- DiProDB: Dinucleotide Property Database ^[52]. The database is designed to collect and analyse thermodynamic, structural and other dinucleotide properties.
- Further details of mathematical and molecular analysis of DNA structure based on X-ray data ^[53]
- Bessel functions corresponding to Fourier transforms of atomic or molecular helices. ^[54]
- Application of X-ray microscopy in analysis of living hydrated cells ^[19]
- overview of STM/AFM/SNOM principles with educative videos ^[55]

Databases for DNA molecular models and sequences

X-ray diffraction

- NDB ID: UD0017 Database ^[13]
- X-ray Atlas -database ^[56]
- PDB files of coordinates for nucleic acid structures from X-ray diffraction by NA (incl. DNA) crystals ^[57]
- Structure factors downloadable files in CIF format ^[58]

Neutron scattering

- ISIS neutron source: ISIS pulsed neutron source: A world centre for science with neutrons & muons at Harwell, near Oxford, UK. ^[59]

X-ray microscopy

- Application of X-ray microscopy in the analysis of living hydrated cells ^[19]

Electron microscopy

- DNA under electron microscope ^[153]

Genomic and structural databases

- CBS Genome Atlas Database ^[60] — contains examples of base skews.
- The Z curve database of genomes — a 3-dimensional visualization and analysis tool of genomes ^[61].
- DNA and other nucleic acids' molecular models: Coordinate files of nucleic acids molecular structure models in PDB and CIF formats ^[62]

Atomic force microscopy

- How SPM Works ^[63]
 - SPM Image Gallery - AFM STM SEM MFM NSOM and more. ^[64]
-

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DNA structure

Nucleic acid structure refers to the structure of nucleic acids such as DNA and RNA. It is often divided into four different levels:

- Primary structure—the raw sequence of nucleobases of each of the component DNA strands;
- Secondary structure—the set of interactions between bases, i.e., which parts of which strands are bound to each other;
- Tertiary structure—the locations of the atoms in three-dimensional space, taking into consideration geometrical and steric constraints; and
- Quaternary structure—the higher-level organization of DNA in chromatin, or to the interactions between separate RNA units in the ribosome or spliceosome.

DNA structure

The structure of DNA shows a variety of forms, both double-stranded and single-stranded. The mechanical properties of DNA, which are directly related to its structure, are a significant problem for cells. Every process which binds or reads DNA is able to use or modify the mechanical properties of DNA for purposes of recognition, packaging and modification. The extreme length (a chromosome may contain a 10 cm long DNA strand), relative rigidity and helical structure of DNA has led to the evolution of histones and of enzymes such as topoisomerases and helicases to manage a cell's DNA. The properties of DNA are closely related to its molecular structure and sequence, particularly the weakness of the hydrogen bonds and electronic interactions that hold strands of DNA together compared to the strength of the bonds within each strand.

Experimental techniques which can directly measure the mechanical properties of DNA are relatively new, and high-resolution visualization in solution is often difficult. Nevertheless, scientists have uncovered large amount of data on the mechanical properties of this polymer, and the implications of DNA's mechanical properties on cellular processes is a topic of active current research.

The DNA found in many cells can be macroscopic in length - a few centimetres long for each human chromosome. Consequently, cells must compact or "package" DNA to carry it within them. In eukaryotes this is carried by spool-like proteins known as histones, around which DNA winds. It is the further compaction of this DNA-protein complex which produces the well known mitotic eukaryotic chromosomes.

See also

- Nucleic acid structure determination (experimental)
 - Nucleic acid structure prediction (computational)
 - Nucleic acid design
 - DNA nanotechnology
 - Nucleic acid thermodynamics
 - DNA supercoil
-

Paracrystalline

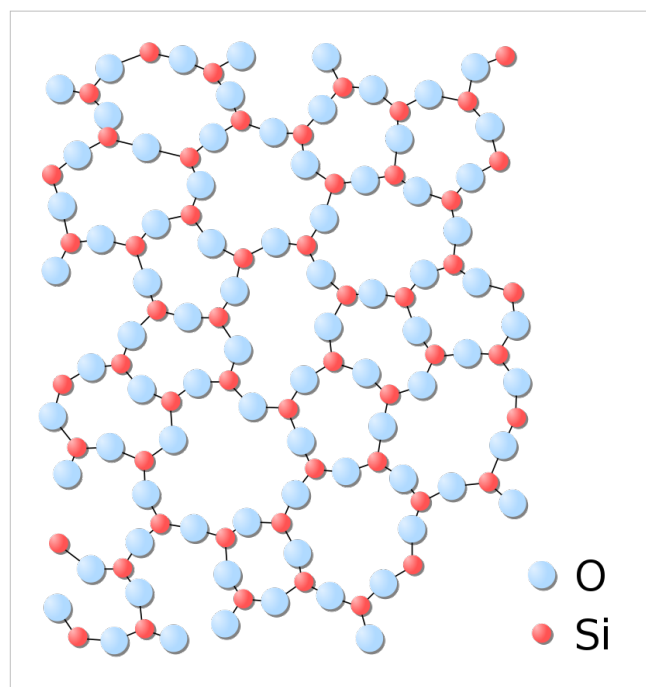
Paracrystalline materials are defined as having short and medium range ordering in their lattice (similar to the liquid crystal phases) but lacking long-range ordering at least in one direction.^[1]

Ordering is the regularity in which atoms appear in a predictable lattice, as measured from one point. In a highly ordered, perfectly crystalline material, or single crystal, the location of every atom in the structure can be described exactly measuring out from a single origin. Conversely, in a disordered structure such as a liquid or amorphous solid, the location of the first and perhaps second nearest neighbors can be described from an origin (with some degree of uncertainty) and the ability to predict locations decreases rapidly from there out. The distance at which atom locations can be predicted is referred to as the correlation length ξ . A paracrystalline material exhibits correlation somewhere between the fully amorphous and fully crystalline.

The primary, most accessible source of crystallinity information is X-ray diffraction, although other techniques may be needed to observe the complex structure of paracrystalline materials, such as fluctuation electron microscopy^[2] in combination with Density of states modeling^[3] of electronic and vibrational states.

Paracrystalline Model

The paracrystalline model is a revision of the Continuous Random Network model first proposed by W. H. Zachariasen in 1932^[4]. The paracrystal model is defined as highly strained, microcrystalline grains surrounded by fully amorphous material^[5]. This is a higher energy state than the continuous random network model. The important distinction between this model and the microcrystalline phases is the lack of defined grain boundaries and highly strained lattice parameters, which makes calculations of molecular and lattice dynamics difficult. A general theory of paracrystals has been formulated in a basic textbook^[6], and then further developed/refined by various authors. An example of a paracrystalline, or partially disordered lattice is shown in the following figure.



Applications

The paracrystal model has been useful, for example, in describing the state of partially amorphous semiconductor materials after deposition. It has also been successfully applied to synthetic polymers, liquid crystals, biopolymers^{[7] [8]}, and biomembranes^[9].

See also

- X-ray scattering
- Amorphous solid
- Single Crystal
- Polycrystalline
- Crystallography
- DNA
- X-ray pattern of a B-DNA Paracrystal^[10]

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Genomics

Genomics is the study of the genomes of organisms. The field includes intensive efforts to determine the entire DNA sequence of organisms and fine-scale genetic mapping efforts. The field also includes studies of intragenomic phenomena such as heterosis, epistasis, pleiotropy and other interactions between loci and alleles within the genome. In contrast, the investigation of the roles and functions of single genes is a primary focus of molecular biology or genetics and is a common topic of modern medical and biological research. Research of single genes does not fall into the definition of genomics unless the aim of this genetic, pathway, and functional information analysis is to elucidate its effect on, place in, and response to the entire genome's networks.

For the United States Environmental Protection Agency, "the term "genomics" encompasses a broader scope of scientific inquiry associated technologies than when genomics was initially considered. A genome is the sum total of all an individual organism's genes. Thus, genomics is the study of all the genes of a cell, or tissue, at the DNA (genotype), mRNA (transcriptome), or protein (proteome) levels."^[1]

History

Genomics was established by Fred Sanger when he first sequenced the complete genomes of a virus and a mitochondrion. His group established techniques of sequencing, genome mapping, data storage, and bioinformatic analyses in the 1970-1980s. A major branch of genomics is still concerned with sequencing the genomes of various organisms, but the knowledge of full genomes has created the possibility for the field of functional genomics, mainly concerned with patterns of gene expression during various conditions. The most important tools here are microarrays and bioinformatics. Study of the full set of proteins in a cell type or tissue, and the changes during various conditions, is called proteomics. A related concept is materiomics, which is defined as the study of the material properties of biological materials (e.g. hierarchical protein structures and materials, mineralized biological tissues, etc.) and their effect on the macroscopic function and failure in their biological context, linking processes, structure and properties at multiple scales through a materials science approach. The actual term 'genomics' is thought to have been coined by Dr. Tom Roderick, a geneticist at the Jackson Laboratory (Bar Harbor, ME) over beer at a meeting held in Maryland on the mapping of the human genome in 1986.

In 1972, Walter Fiers and his team at the Laboratory of Molecular Biology of the University of Ghent (Ghent, Belgium) were the first to determine the sequence of a gene: the gene for Bacteriophage MS2 coat protein.^[2] In 1976, the team determined the complete nucleotide-sequence of bacteriophage MS2-RNA.^[3] The first DNA-based genome to be sequenced in its entirety was that of bacteriophage Φ -X174; (5,368 bp), sequenced by Frederick Sanger in 1977.^[4]

The first free-living organism to be sequenced was that of *Haemophilus influenzae* (1.8 Mb) in 1995, and since then genomes are being sequenced at a rapid pace.

As of September 2007, the complete sequence was known of about 1879 viruses ^[5], 577 bacterial species and roughly 23 eukaryote organisms, of which about half are fungi. ^[6] Most of the bacteria whose genomes have been completely sequenced are problematic disease-causing agents, such as *Haemophilus influenzae*. Of the other sequenced species, most were chosen because they were well-studied model organisms or promised to become good models. Yeast (*Saccharomyces cerevisiae*) has long been an important model organism for the eukaryotic cell, while the fruit fly *Drosophila melanogaster* has been a very important tool (notably in early pre-molecular genetics). The worm *Caenorhabditis elegans* is an often used simple model for multicellular organisms. The zebrafish *Brachydanio rerio* is used for many developmental studies on the molecular level and the flower *Arabidopsis thaliana* is a model organism for flowering plants. The Japanese pufferfish (*Takifugu rubripes*) and the spotted green pufferfish (*Tetraodon nigroviridis*) are interesting because of their small and compact genomes, containing very little non-coding DNA compared to most species. ^[7] ^[8] The mammals dog (*Canis familiaris*), ^[9] brown rat (*Rattus*

norvegicus), mouse (*Mus musculus*), and chimpanzee (*Pan troglodytes*) are all important model animals in medical research.

Human genomics

A rough draft of the human genome was completed by the Human Genome Project in early 2001, creating much fanfare. By 2007 the human sequence was declared "finished" (less than one error in 20,000 bases and all chromosomes assembled. Display of the results of the project required significant bioinformatics resources. The sequence of the human reference assembly can be explored using the UCSC Genome Browser.

Bacteriophage genomics

Bacteriophages have played and continue to play a key role in bacterial genetics and molecular biology. Historically, they were used to define gene structure and gene regulation. Also the first genome to be sequenced was a bacteriophage. However, bacteriophage research did not lead the genomics revolution, which is clearly dominated by bacterial genomics. Only very recently has the study of bacteriophage genomes become prominent, thereby enabling researchers to understand the mechanisms underlying phage evolution. Bacteriophage genome sequences can be obtained through direct sequencing of isolated bacteriophages, but can also be derived as part of microbial genomes. Analysis of bacterial genomes has shown that a substantial amount of microbial DNA consists of prophage sequences and prophage-like elements. A detailed database mining of these sequences offers insights into the role of prophages in shaping the bacterial genome.^[10]

Cyanobacteria genomics

At present there are 24 cyanobacteria for which a total genome sequence is available. 15 of these cyanobacteria come from the marine environment. These are six *Prochlorococcus* strains, seven marine *Synechococcus* strains, *Trichodesmium erythraeum* IMS101 and *Crocospaera watsonii* WH8501. Several studies have demonstrated how these sequences could be used very successfully to infer important ecological and physiological characteristics of marine cyanobacteria. However, there are many more genome projects currently in progress, amongst those there are further *Prochlorococcus* and marine *Synechococcus* isolates, *Acaryochloris* and *Prochloron*, the N₂-fixing filamentous cyanobacteria *Nodularia spumigena*, *Lyngbya aestuarii* and *Lyngbya majuscula*, as well as bacteriophages infecting marine cyanobacteria. Thus, the growing body of genome information can also be tapped in a more general way to address global problems by applying a comparative approach. Some new and exciting examples of progress in this field are the identification of genes for regulatory RNAs, insights into the evolutionary origin of photosynthesis, or estimation of the contribution of horizontal gene transfer to the genomes that have been analyzed.^[11]

See also

- Full Genome Sequencing
 - Computational genomics
 - Nitrogenomics
 - Metagenomics
 - Predictive Medicine
 - Personal genomics
 - Psychogenomics
-

External links

- Genomics Directory ^[12]: A one-stop biotechnology resource center for bioentrepreneurs, scientists, and students
- Annual Review of Genomics and Human Genetics ^[13]
- BMC Genomics ^[14]: A BMC journal on Genomics
- Genomics ^[15]: UK companies and laboratories* Genomics journal ^[16]
- Genomics.org ^[17]: An openfree wiki based Genomics portal
- NHGRI ^[18]: US government's genome institute
- Pharmacogenomics in Drug Discovery and Development ^[19], a book on pharmacogenomics, diseases, personalized medicine, and therapeutics
- Tishchenko P. D. Genomics: New Science in the New Cultural Situation ^[20]
- Undergraduate program on Genomic Sciences (spanish) ^[21]: One of the first undergraduate programs in the world
- JCVI Comprehensive Microbial Resource ^[22]
- Pathema: A Clade Specific Bioinformatics Resource Center ^[23]
- KoreaGenome.org ^[24]: The first Korean Genome published and the sequence is available freely.
- GenomicsNetwork ^[25]: Looks at the development and use of the science and technologies of genomics.
- Institute for Genome Science ^[26]: Genomics research.

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Computational genomics

Computational genomics refers to the use of computational analysis to decipher biology from genome sequences and related data^[1], including both DNA and RNA sequence as well as other "post-genomic" data (i.e. experimental data obtained with technologies that require the genome sequence, such as genomic DNA microarrays). As such, computational genomics may be regarded as a subset of bioinformatics, but with a focus on using whole genomes (rather than individual genes) to understand the principles of how the DNA of a species controls its biology at the molecular level and beyond. With the current abundance of massive biological datasets, computational studies have become one of the most important means to biological discovery.^[2]

History

The roots of computational genomics are shared with those of bioinformatics. During the 1960s, Margaret Dayhoff and others at the National Biomedical Research Foundation assembled databases of homologous protein sequences for evolutionary study.^[3] Their research developed a phylogenetic tree that determined the evolutionary changes that were required for a particular protein to change into another protein based on the underlying amino acid sequences. This led them to create a scoring matrix that assessed the likelihood of one protein being related to another.

Beginning in the 1980s, databases of genome sequences began to be recorded, but this presented new challenges in the form of searching and comparing the databases of gene information. Unlike text-searching algorithms that are used on websites such as google or Wikipedia, searching for sections of genetic similarity requires one to find strings that are not simply identical, but similar. This led to the development of the Needleman-Wunsch algorithm, which is a dynamic programming algorithm for comparing sets of amino acid sequences with each other by using scoring matrices derived from the earlier research by Dayhoff. Later, the BLAST algorithm was developed for performing fast, optimized searches of gene sequence databases. BLAST and its derivatives are probably the most widely-used algorithms for this purpose.^[4]

The emergence of the phrase "computational genomics" coincides with the availability of complete sequenced genomes in the mid-to-late 1990's. The first meeting of the Annual Conference on Computational Genomics was organized by scientists from The Institute for Genomic Research (TIGR) in 1998, providing a forum for this speciality and effectively distinguishing this area of science from the more general fields of Genomics or Computational Biology.^[5]^[6] The first use of this term in scientific literature, according to MEDLINE abstracts, was just one year earlier in Nucleic Acids Research.^[7] The final Computational Genomics conference was held in 2006, featuring a keynote talk by Nobel Laureate Barry Marshall, co-discoverer of the link between *Helicobacter pylori* and stomach ulcers. As of 2010, the leading conferences in the field include Intelligent Systems for Molecular Biology (ISMB), RECOMB, and the Cold Spring Harbor Laboratory and Sanger Institute's meetings titled "Biology of Genomes" and "Genome Informatics".

The development of computer-assisted mathematics (using products such as Mathematica or Matlab) has helped engineers, mathematicians and computer scientists to start operating in this domain, and a public collection of case studies and demonstrations is growing, ranging from whole genome comparisons to gene expression analysis.^[8] This has increased the introduction of different ideas, including concepts from systems and control, information theory, strings analysis and data mining. It is anticipated that computational approaches will become and remain a standard topic for research and teaching, while students fluent in both topics start being formed in the multiple courses created in the past few years.

Contributions of computational genomics research to biology

Contributions of computational genomics research to biology include ^[2] :

- discovering subtle patterns in genomic sequences
- proposing cellular signalling networks
- proposing mechanisms of genome evolution
- predict precise locations of all human genes using comparative genomics techniques with several mammalian and vertebrate species
- predict conserved genomic regions that are related to early embryonic development
- discover potential links between repeated sequence motifs and tissue-specific gene expression
- measure regions of genomes that have undergone unusually rapid evolution

See also

- Bioinformatics
- Biowiki
- Computational biology
- Genomics
- Microarray
- BLAST
- Computational epigenetics

External links

- Harvard Extension School Biophysics 101, Genomics and Computational Biology, <http://www.courses.fas.harvard.edu/~bphys101/info/syllabus.html>
- University of Bristol course in Computational Genomics, <http://www.computational-genomics.net/>

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Interactomics

Interactomics is a discipline at the intersection of bioinformatics and biology that deals with studying both the interactions and the consequences of those interactions between and among proteins, and other molecules within a cell^[1]. The network of all such interactions is called the Interactome. Interactomics thus aims to compare such networks of interactions (i.e., interactomes) between and within species in order to find how the traits of such networks are either preserved or varied. From a mathematical, or mathematical biology viewpoint an interactome network is a graph or a category representing the most important interactions pertinent to the normal physiological functions of a cell or organism.

Interactomics is an example of "top-down" systems biology, which takes an overhead, as well as overall, view of a biosystem or organism. Large sets of genome-wide and proteomic data are collected, and correlations between different molecules are inferred. From the data new hypotheses are formulated about feedbacks between these molecules. These hypotheses can then be tested by new experiments^[2].

Through the study of the interaction of all of the molecules in a cell the field looks to gain a deeper understanding of genome function and evolution than just examining an individual genome in isolation^[1]. Interactomics goes beyond cellular proteomics in that it not only attempts to characterize the interaction between proteins, but between all molecules in the cell.

Methods of interactomics

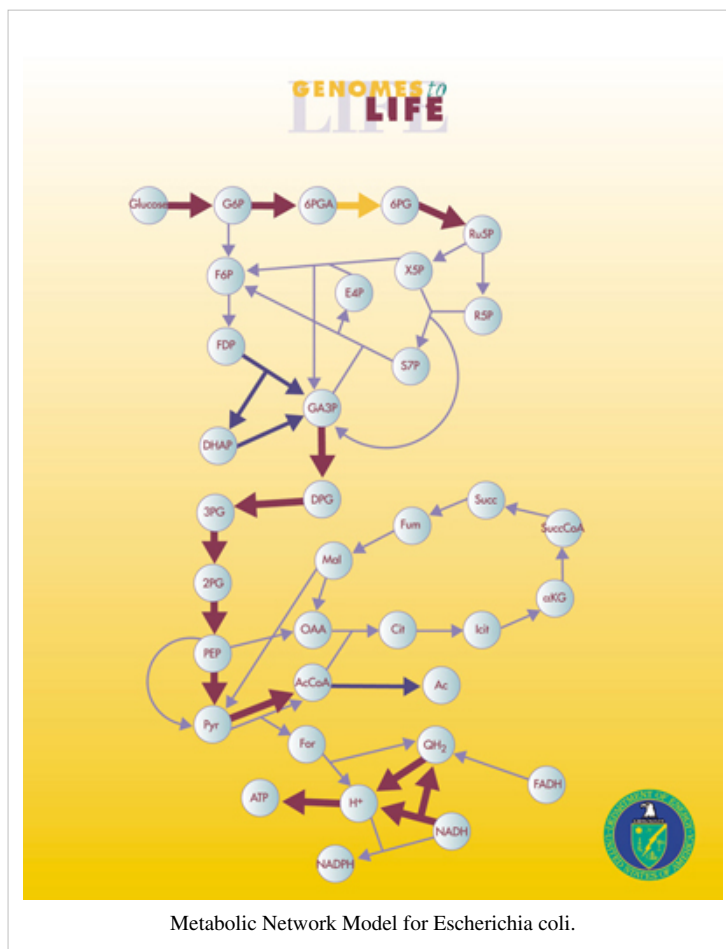
The study of the interactome requires the collection of large amounts of data by way of high throughput experiments. Through these experiments a large number of data points are collected from a single organism under a small number of perturbations^[2] These experiments include:

- Two-hybrid screening
 - Tandem Affinity Purification
 - X-ray tomography
 - Optical fluorescence microscopy
-

Recent developments

The field of interactomics is currently rapidly expanding and developing. While no biological interactomes have been fully characterized. Over 90% of proteins in *Saccharomyces cerevisiae* have been screened and their interactions characterized, making it the first interactome to be nearly fully specified^[3].

Also there have been recent systematic attempts to explore the human interactome^[1] and^[4].



Other species whose interactomes have been studied in some detail include *Caenorhabditis elegans* and *Drosophila melanogaster*.

Criticisms and concerns

Kiemer and Cesareni^[1] raise the following concerns with the current state of the field:

- The experimental procedures associated with the field are error prone leading to "noisy results". This leads to 30% of all reported interactions being artifacts. In fact, two groups using the same techniques on the same organism found less than 30% interactions in common.
- Techniques may be biased, i.e. the technique determines which interactions are found.
- Interactomes are not nearly complete with perhaps the exception of *S. cerevisiae*.
- While genomes are stable, interactomes may vary between tissues and developmental stages.
- Genomics compares amino acids, and nucleotides which are in a sense unchangeable, but interactomics compares proteins and other molecules which are subject to mutation and evolution.
- It is difficult to match evolutionarily related proteins in distantly related species.

See also

- Interaction network
- Proteomics
- Metabolic network
- Metabolic network modelling
- Metabolic pathway
- Genomics
- Mathematical biology
- Systems biology

External links

- Interactomics.org^[5]. A dedicated interactomics web site operated under BioLicense.
- Interactome.org^[6]. An interactome wiki site.
- PSIBase^[7] Structural Interactome Map of all Proteins.
- Omics.org^[8]. An omics portal site that is openfree (under BioLicense)
- Genomics.org^[17]. A Genomics wiki site.
- Comparative Interactomics analysis of protein family interaction networks using PSIMAP (protein structural interactome map)^[9]
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DNA nanotechnology

Part of a series of articles on
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DNA nanotechnology is a branch of nanotechnology which uses the unique molecular recognition properties of DNA and other nucleic acids to create designed, controllable structures out of DNA. This has possible applications in molecular self-assembly and in DNA computing. In this field, DNA is used as a structural material rather than as a carrier of genetic information, making it an example of bionanotechnology.

History



The M. C. Escher woodcut *Depth* (pictured) inspired Nadrian Seeman to consider using three-dimensional lattices of DNA to orient hard-to-crystallize molecules.

This led to the beginning of the field of DNA nanotechnology.

The concept of DNA nanotechnology was invented by Nadrian Seeman in early 1980s.^[1] A crystallographer, Seeman was frustrated with the haphazardness and guesswork involved with crystallizing certain molecules. In fall 1980, while at a campus pub, Seeman was inspired by the M. C. Escher woodcut *Depth* to realize that a three-dimensional DNA lattice could be used to orient target molecules, simplifying their crystallographic study.^[2] In 1991, Seeman's laboratory published the synthesis of a cube made of DNA, the first three-dimensional nanoscale object, for which he received the 1995 Feynman Prize in Nanotechnology, which was followed by a DNA truncated octahedron. However, it soon became clear that these objects were not rigid enough to form three-dimensional lattices.^{[1] [2]}

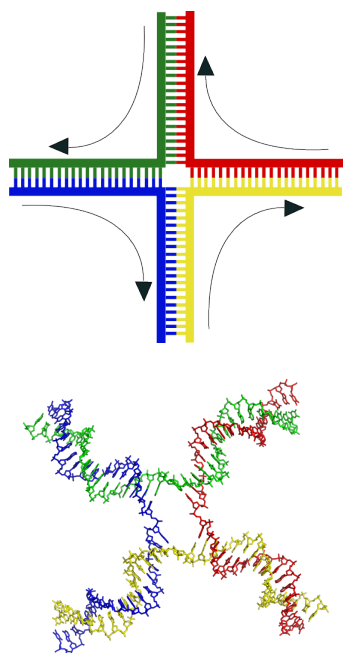
Seeman developed the more rigid "DX" motif, and in collaboration with Erik Winfree, in 1998 published the creation of two-dimensional lattices of DX tiles. These tile-based structures had the advantage that they provided the capability to implement DNA computing, which was demonstrated by Winfree and Paul Rothemund in 2004, and for which they shared the 2006 Feynman Prize in Nanotechnology.^{[1] [2]}

The field has continued to branch out. The first DNA nanomachine—a motif which changes its structure in response to an input—was demonstrated in 1999. Nanoarchitecture, first proposed by Seeman in 1987, was beginning to be demonstrated by 2006. Also in 2006, Rothemund first demonstrated the new DNA origami technique for easily and robustly creating folded DNA molecules of any shape. In 2009, Seeman published the synthesis of a three-dimensional lattice, nearly thirty years after he had set out to do so.

Fundamental concepts

DNA nanotechnology makes use of branched DNA structures to create DNA complexes with useful properties. DNA is normally a linear molecule, in that its axis is unbranched. However, DNA molecules containing junctions can also be made. For example, a four-arm junction can be made using four individual DNA strands which are complementary to each other in the correct pattern. Due to Watson-Crick base pairing, only portions of the strands which are complementary to each other will attach to each other to form duplex DNA. This four-arm junction is an immobile form of a Holliday junction.

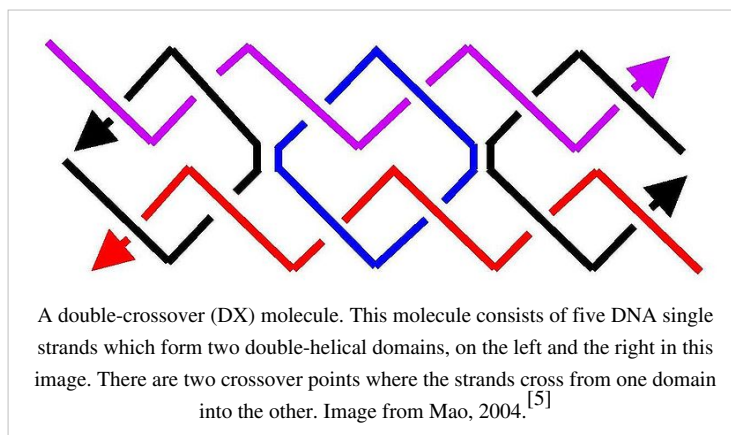
Junctions can be used in more complex molecules. The most important of these is the "double-crossover" or DX motif. Here, two DNA duplexes lie next to each other, and share two junction points where strands cross from one duplex into the other. This molecule has the advantage that the junction points are now constrained to a single orientation as opposed to being flexible as in the four-arm junction. This makes the DX motif suitable as a structural building block for larger DNA complexes.^[2]



Structure of the 4-arm junction.

Left: A schematic. **Right:** A more realistic model.^[4]

Each of the four separate DNA single strands are shown in different colors.



Design

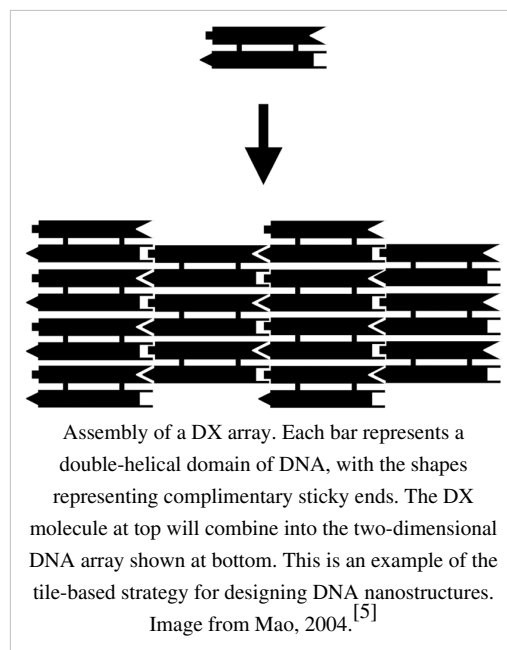
A main goal of DNA nanotechnology is, given a target structure and/or functionality, to determine what sequences of DNA molecules will assemble into that structure. There are a number of different approaches which have been used to design DNA sequences that will form the desired structure.

Tile-based structures

The earliest method for creating DNA nanostructures was to construct them out of smaller discrete units. This method has the advantage of being able to conceptually separate the stronger interactions which form each tile from the assembly of the larger complete structure. It is often used to make periodic lattices, but can also be used to implement algorithmic self-assembly, making them one platform for DNA computing.

Folding structures

An alternative to the tile-based approach, two-dimensional DNA structures can be made from a single, long DNA strand of arbitrary sequence which is folded into the desired shape by using shorter, "staple" strands. This allows the creation of two-dimensional shapes at the nanoscale using DNA. Demonstrated designs have included the smiley face and a coarse map of North America. DNA origami was the cover story of *Nature* on March 15, 2006.^[6]



Kinetic assembly

Most design in DNA nanotechnology only focuses on designing sequences so that the target structure is a thermodynamic minimum, without regard to the assembly pathway. Recently, there has been interest in controlling the kinetics of DNA self-assembly, so that transient dynamics can also be programmed into the assembly. Such a method also has the advantage of proceeding isothermally and thus not requiring a thermal annealing step required by solely thermodynamic approaches.^[7]

Primary sequence design

After any of the above approaches are used to design the secondary structure of a target molecule, an actual sequence of nucleotides must be devised which will form into the desired structure. Nucleic acid design is the process of generating a set of nucleic acid base sequences that will associate into a desired conformation (see, for example, RNA structure). Nucleic acid design is central to the field of DNA nanotechnology.

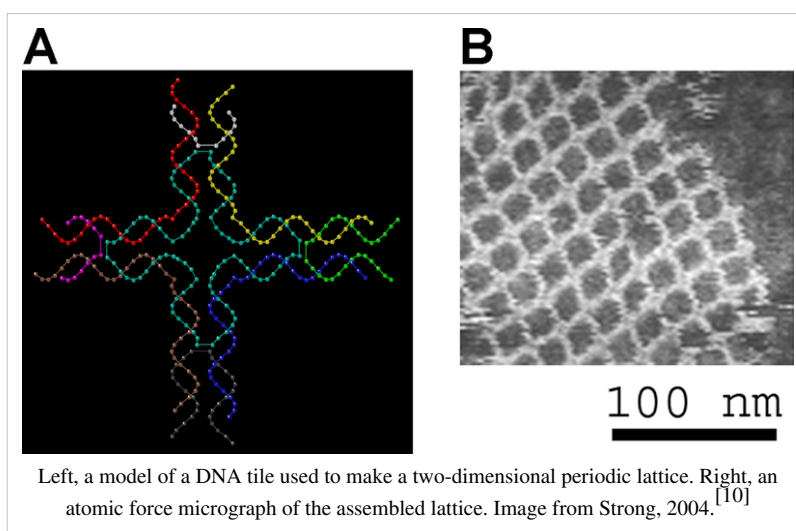
Nucleic acid design has similar goals to protein design: in both, the sequence of monomers is designed to favor the desired folded or associated structure and to disfavor alternate structures. Nucleic acid design has the advantage of being a much computationally simpler problem, since the simplicity of Watson-Crick base pairing rules leads to simple heuristic methods which yield experimentally robust designs. However, nucleic acid structures are less versatile than proteins in their functionality.^{[8] [9]}

Target structures

Many structures made from DNA have been synthesized and characterized.

Two-dimensional lattices

DX, or Double Crossover, molecules can be equipped with sticky ends in order to combine them into a two-dimensional periodic lattice. Each DX molecule has four termini, one at each end of the two double-helical domains, and these can be equipped with sticky ends that program them to combine into a specific pattern. More than one type of DX can be used which can be made to arrange in rows or any other tessellated pattern. They thus form extended flat sheets which are essentially two-dimensional crystals of DNA.^{[11] [12]}



Two-dimensional arrays have been made out of other motifs as well, including the Holliday junction rhombus array as well as various DX-based arrays in the shapes of triangles and hexagons.^{[13] [14] [15]}

Discrete three-dimensional structures

A number of three-dimensional DNA molecules have been made which have the connectivity of a polyhedron such as an octahedron or cube. In other words, the DNA duplexes trace the edges of a polyhedron with a DNA junction at each vertex.

The earliest demonstrations of DNA polyhedra involved multiple ligations and solid-phase synthesis steps to create catenated polyhedra.^[16] More recent work has yielded polyhedra whose synthesis is much easier. These include a DNA truncated octahedron made from a long single strand designed to fold into the correct conformation, as well as a tetrahedron which can be produced from four DNA strands in a single step.^{[17] [18]}

DNA structures with solid faces have also been constructed, using the DNA origami method. These can be programmed to open and release their cargo in response to a stimulus, making them potentially useful as programmable molecular cages.^{[19] [20]}

DNA nanotubes

In addition to flat sheets, DX arrays have been made to form hollow nanotubes of 4-20 nm diameter. These DNA nanotubes are somewhat similar in size and shape to carbon nanotubes, but the carbon nanotubes are stronger and better conductors, whereas the DNA nanotubes are more easily modified and connected to other structures.^[21]

Extended three-dimensional lattices

Creating three-dimensional lattices out of DNA was the earliest goal of DNA nanotechnology, but proved to be one of the most difficult to realize. Success in constructing three-dimensional DNA lattices was finally reported in 2009 using a motif based on the concept of tensegrity, a balance between tension and compression forces.^[22]

Applications

DNA nanotechnology focuses on creating molecules with designed functionalities as well as structures. Many classes of functional systems have been demonstrated.

Nanoarchitecture

The idea of using DNA arrays to template the assembly of other functional molecules was first suggested by Nadrian Seeman in 1987,^[23] but only recently has progress been made in reducing these kinds of schemes to practice. In 2006, researchers covalently attached gold nanoparticles to a DX-based tile and showed that self-assembly of the DNA structures also assembled the nanoparticles hosted on them. A non-covalent hosting scheme was shown in 2007, using Dervan polyamides on a DX array to arrange streptavidin proteins on specific kinds of tiles on the DNA array.^{[24] [25]}

Previously in 2006 LaBean demonstrated the letters "D" "N" and "A" created on a 4x4 DX array using streptavidin.^[26]

DNA has also been used to assemble a single walled carbon nanotube Field-effect transistor.^[27]

Algorithmic self-assembly

DNA nanotechnology has been applied to the related field of DNA computing. The DX tiles can have their sticky end sequences chosen so that they act as Wang tiles, allowing them to perform computation. A DX array has been demonstrated whose assembly encodes an XOR operation; this allows the DNA array to implement a cellular automaton which generates a fractal called the Sierpinski gasket. This shows that computation can be incorporated into the assembly of DNA arrays, increasing its scope beyond simple periodic arrays.

Note that DNA computing overlaps with, but is distinct from, DNA nanotechnology. The latter uses the specificity of Watson-Crick basepairing to make novel structures out of DNA. These structures can be used for DNA computing, but they do not have to be. Additionally, DNA computing can be done without using the types of molecules made possible by DNA nanotechnology.^[28]

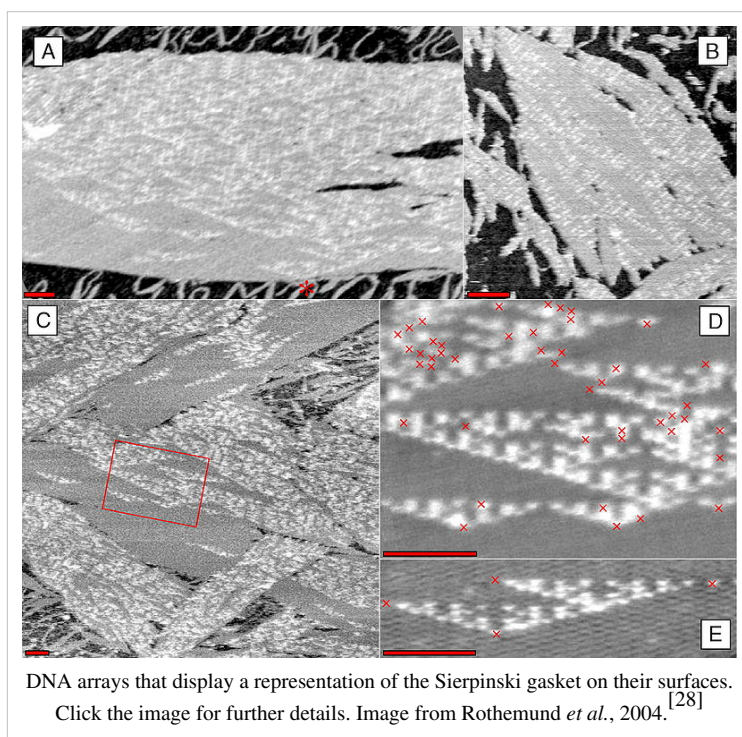
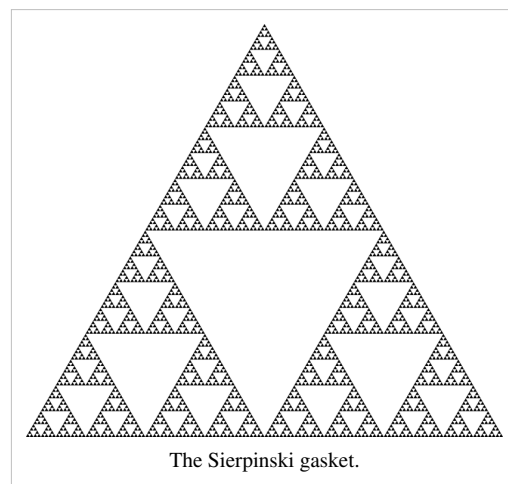
Logic circuits

A design called a *stem loop*, consisting of a single strand of DNA which has a loop at an end, are a dynamic structure that opens and closes when a piece of DNA bonds to the loop part. This effect has been exploited to create several logic gates. These logic gates have been used to create the computers MAYA I and MAYA II which can play tic-tac-toe to some extent.^[29]

DNA nanomechanical devices

DNA complexes have been made which change their conformation upon some stimulus. These are intended to have applications in nanorobotics. One of the first such devices, called "molecular tweezers," changes from an open to a closed state based upon the presence of control strands.

DNA machines have also been made which show a twisting motion. One of these makes use of the transition between the B-DNA and Z-DNA forms to respond to a change in buffer conditions. Another relies on the presence of control strands to switch from a paranemic-crossover (PX) conformation to a double-junction (JX2) conformation.^{[30] [31] [32]}



Materials and methods

DNA of custom sequence is readily available through oligonucleotide synthesis. This process is usually automated by using a DNA synthesizing machine, and custom DNA is commercially available from many vendors.

The sequences of the individual DNA strands which make up the target structure are designed computationally. Molecular modelling and thermodynamic modelling are sometimes used to optimize the DNA sequences.

The DNA molecules created by DNA nanotechnology are usually characterized by gel electrophoresis, which provides information about the size and shape of DNA molecules, indicating whether they have formed properly. Fluorescent labelling and Fluorescence resonance energy transfer are also used to characterize the structure of the molecules.

DNA structures can be directly imaged by atomic force microscopy, which images structures deposited on a flat surface. This method is well-suited to extended two-dimensional structures, but is less useful for discrete three-dimensional structures. For these latter structures cryo-electron microscopy is gaining popularity as an important method. Extended three-dimensional lattices are analyzed by X-ray crystallography.

See also

- DNA structure
- Molecular models of DNA

References

Note: Click on the doi to access the text of the referenced article.

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Further reading

Following is a list of review articles and books which can further introduce the reader to the field of DNA nanotechnology.

- Seeman, Nadrian C. (June 2004). "Nanotechnology and the double helix" (<http://www.scientificamerican.com/article.cfm?id=nanotechnology-and-the-do>). *Scientific American* **290** (6): 64–75. doi:10.1038/scientificamerican0604-64. PMID 15195395.—An article written for laypeople by the founder of the field.
- Pelesko, John A. (2007). "Chapter 8: DNA Self-Assembly". *Self-assembly: the science of things that put themselves together*. New York: Chapman & Hall/CRC. ISBN 978 1 58488 687 7.—An overview of the results of

the field from the perspective of self-assembly.

- Seeman, Nadrian C. (1 November 1999). "DNA Engineering and its Application to Nanotechnology". *Trends in Biotechnology* **17** (11): 437–443. doi:10.1016/S0167-7799(99)01360-8. ISSN 0167-7799.—An older review containing a good description of the motivation behind DNA technology.
- Seeman, Nadrian C. (2007). "An Overview of Structural DNA Nanotechnology". *Molecular Biotechnology* **37** (3): 246. doi:10.1007/s12033-007-0059-4. PMID 17952671.—A more recent review.
- Feldkamp, Udo; Niemeyer, Christof M. (2006). "Rational Design of DNA Nanoarchitectures". *Angewandte Chemie International Edition* **45**: 1856. doi:10.1002/anie.200502358.—A good review coming from the viewpoint of secondary structure design.
- Lin, Chenxiang; Liu, Yan; Rinker, Sherri; Yan, Hao (2006). "DNA Tile Based Self-Assembly: Building Complex Nanoarchitectures". *ChemPhysChem* **7**: 1641. doi:10.1002/cphc.200600260.—A minireview specifically focusing on tile-based assembly.
- Chen, Junghuei; Jonoska, Natasha; Rozenberg, Grzegorz, eds (2006). *Nanotechnology: Science and Computation*. Natural Computing Series. New York: Springer. ISBN 978 3 540 30295 7.—A book containing articles by many researchers on DNA nanotechnology and DNA computing.

External links

- Jørgen Kjems lab at Aarhus University (<http://www.rnai.dk/>)
- Thom LaBean lab at Duke University (<http://www.cs.duke.edu/~thl/>)
- Dan Luo lab at Cornell University (<http://luolabs.bee.cornell.edu>)
- Chengde Mao page at Purdue University (<http://www.chem.purdue.edu/people/faculty/faculty.asp?itemID=46>)
- John Reif lab at Duke University (<http://www.cs.duke.edu/~reif/BMC/Reif.BMCproject.html>)
- Nadrian Seeman lab at NYU (<http://seemanlab4.chem.nyu.edu/>)
- William M. Shih lab at Harvard Medical School (http://research2.dfci.harvard.edu/shih/SHIH_LAB/Home.html)
- Hanadi Sleiman lab at McGill University (<http://www.hanadisleiman.com>)
- Andrew Turberfield lab at Oxford University (<http://www.physics.ox.ac.uk/cm/people/turberfield.htm>)
- Erik Winfree lab at Caltech (<http://dna.caltech.edu/>)
- Hao Yan lab at Arizona State University (http://chemistry.asu.edu/faculty/hao_yan.asp)
- Peng Yin lab at Harvard Medical School (<http://www.yinlab.org>)
- Bernard Yurke formerly at Bell Labs (<http://www.bell-labs.com/org/physicalsciences/profiles/yurke.html>) now at Boise State University (<http://coen.boisestate.edu/departments/faculty.asp?ID=134>)
- International Society for Nanoscale Science, Computation and Engineering (<http://www.isnsce.org/>)
- Software for 3D DNA design, modeling and/or simulation:
 - Ascalaph Designer (http://www.biomolecular-modeling.com/Ascalaph/Ascalaph_Designer.html)
 - caDNAno (<http://cadnano.org>)
 - GIDEON (<http://www.subirac.com>)
 - NanoEngineer-1 (<http://www.nanoengineer-1.net>)
- Nanohedron.com (<http://www.nanohedron.com>) images of DNA self assemblies

DNA computing

DNA computing is a form of computing which uses DNA, biochemistry and molecular biology, instead of the traditional silicon-based computer technologies. DNA computing, or, more generally, molecular computing, is a fast developing interdisciplinary area. Research and development in this area concerns theory, experiments and applications of DNA computing.

History

This field was initially developed by Leonard Adleman of the University of Southern California, in 1994.^[1] Adleman demonstrated a proof-of-concept use of DNA as a form of computation which solved the seven-point Hamiltonian path problem. Since the initial Adleman experiments, advances have been made and various Turing machines have been proven to be constructible.^{[2] [3]}

In 2002, researchers from the Weizmann Institute of Science in Rehovot, Israel, unveiled a programmable molecular computing machine composed of enzymes and DNA molecules instead of silicon microchips.^[4] On April 28, 2004, Ehud Shapiro, Yaakov Benenson, Binyamin Gil, Uri Ben-Dor, and Rivka Adar at the Weizmann Institute announced in the journal *Nature* that they had constructed a DNA computer coupled with an input and output module which would theoretically be capable of diagnosing cancerous activity within a cell, and releasing an anti-cancer drug upon diagnosis.^[5]

Capabilities

DNA computing is fundamentally similar to parallel computing in that it takes advantage of the many different molecules of DNA to try many different possibilities at once.^[6]

DNA computing also offers much lower power consumption than traditional silicon computers. DNA uses adenosine triphosphate (ATP) as fuel to allow ligation or as a means to heat the strand to cause disassociation.^[7] Both strand hybridization and the hydrolysis of the DNA backbone can occur spontaneously, powered by the potential energy stored in DNA. Consumption of two ATP molecules releases 1.5×10^{-19} J. Even with a large number of transitions per second using two ATP molecules, power output is still low. For instance, Kahan reports 109 transitions per second with an energy consumption of 10^{-10} W,^[8] and similarly Shapiro reports a system producing 7.5×10^{11} outputs in 4000 sec resulting in an energy consumption rate of $\sim 10^{-10}$ W.^[9]

For certain specialized problems, DNA computers are faster and smaller than any other computer built so far. Furthermore, particular mathematical computations have been demonstrated to work on a DNA computer. As an example, Aran Nayeibi^[10] has provided a general scalable implementation of Strassen's matrix multiplication algorithm on a DNA computer.

But DNA computing does not provide any new capabilities from the standpoint of computability theory, the study of which problems are computationally solvable using different models of computation. For example, if the space required for the solution of a problem grows exponentially with the size of the problem (EXPSpace problems) on von Neumann machines, it still grows exponentially with the size of the problem on DNA machines. For very large EXPSpace problems, the amount of DNA required is too large to be practical. (Quantum computing, on the other hand, *does* provide some interesting new capabilities.)

DNA computing overlaps with, but is distinct from, DNA nanotechnology. The latter uses the specificity of Watson-Crick basepairing and other DNA properties to make novel structures out of DNA. These structures can be used for DNA computing, but they do not have to be. Additionally, DNA computing can be done without using the types of molecules made possible by DNA nanotechnology.

Methods

There are multiple methods for building a computing device based on DNA, each with its own advantages and disadvantages. Most of these build the basic logic gates (AND, OR, NOT) associated with digital logic from a DNA basis. Some of the different bases include DNAzymes, deoxyoligonucleotides, enzymes, DNA tiling, and polymerase chain reaction.

DNAzymes

Catalytic DNA (deoxyribozyme or DNAzyme) catalyze a reaction when interacting with the appropriate input, such as a matching oligonucleotide. These DNAzymes are used to build logic gates analogous to digital logic in silicon; however, DNAzymes are limited to 1-, 2-, and 3-input gates with no current implementation for evaluating statements in series.

The DNAzyme logic gate changes its structure when it binds to a matching oligonucleotide and the fluorogenic substrate it is bonded to is cleaved free. While other materials can be used, most models use a fluorescence-based substrate because it is very easy to detect, even at the single molecule limit.^[11] The amount of fluorescence can then be measured to tell whether or not a reaction took place. The DNAzyme that changes is then “used,” and cannot initiate any more reactions. Because of this, these reactions take place in a device such as a continuous stirred-tank reactor, where old product is removed and new molecules added.

Two commonly used DNAzymes are named E6 and 8-17. These are popular because they allow cleaving of a substrate in any arbitrary location.^[12] Stojanovic and MacDonald have used the E6 DNAzymes to build the MAYA I^[13] and MAYA II^[14] machines, respectively; Stojanovic has also demonstrated logic gates using the 8-17 DNAzyme.^[15] While these DNAzymes have been demonstrated to be useful for constructing logic gates, they are limited by the need for a metal cofactor to function, such as Zn^{2+} or Mn^{2+} , and thus are not useful *in vivo*.^[11] [16]

Enzymes

Enzyme based DNA computers are usually of the form of a simple Turing machine; there is analogous hardware, in the form of an enzyme, and software, in the form of DNA.^[17]

Shapiro has demonstrated a DNA computer using the FokI enzyme^[9] and expanded on his work by going on to show automata that diagnose and react to prostate cancer: under expression of the genes PPAP2B and GSTP1 and an over expression of PIM1 and HPN.^[5] His automata evaluated the expression of each gene, one gene at a time, and on positive diagnosis then released a single strand DNA molecule (ssDNA) that is an antisense for MDM2. MDM2 is a repressor of protein 53, which itself is a tumor suppressor.^[18] On negative diagnosis it was decided to release a suppressor of the positive diagnosis drug instead of doing nothing. A limitation of this implementation is that two separate automata are required, one to administer each drug. The entire process of evaluation until drug release took around an hour to complete. This method also requires transition molecules as well as the FokI enzyme to be present. The requirement for the FokI enzyme limits application *in vivo*, at least for use in “cells of higher organisms”.^[8] It should also be pointed out that the 'software' molecules can be reused in this case.

Toehold exchange

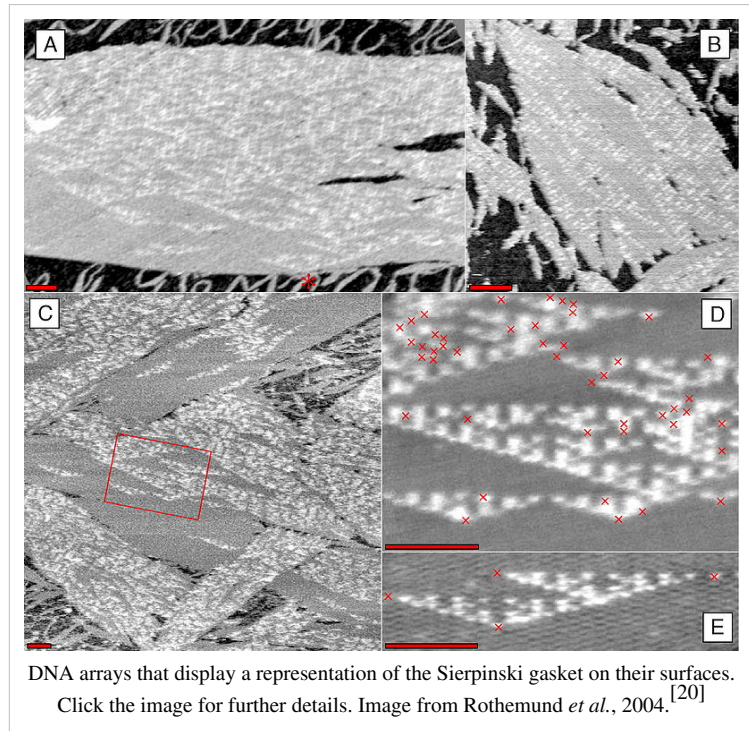
DNA computers have also been constructed using the concept of toehold exchange. In this system, an input DNA strand binds to a sticky end, or toehold, on another DNA molecule, which allows it to displace another strand segment from the molecule. This allows the creation of modular logic components such as AND, OR, and NOT gates and signal amplifiers, which can be linked into arbitrarily large computers. This class of DNA computers does not require enzymes or any chemical capability of the DNA.^[19]

Algorithmic self-assembly

DNA nanotechnology has been applied to the related field of DNA computing. DNA tiles can be designed to contain multiple sticky ends with sequences chosen so that they act as Wang tiles. A DX array has been demonstrated whose assembly encodes an XOR operation; this allows the DNA array to implement a cellular automaton which generates a fractal called the Sierpinski gasket. This shows that computation can be incorporated into the assembly of DNA arrays, increasing its scope beyond simple periodic arrays.^[20]

See also

- Biocomputers
- Computational gene
- Molecular electronics
- Peptide computing
- Parallel computing
- Quantum computing



Further reading

- Martyn Amos (June 2005). *Theoretical and Experimental DNA Computation*^[21]. Springer. ISBN 3-540-65773-8. — The first general text to cover the whole field.
- Gheorge Paun, Grzegorz Rozenberg, Arto Salomaa (October 1998). *DNA Computing - New Computing Paradigms*. Springer-Verlag. ISBN 3-540-64196-3. — The book starts with an introduction to DNA-related matters, the basics of biochemistry and language and computation theory, and progresses to the advanced mathematical theory of DNA computing.
- JB. Waldner (January 2007). *Nanocomputers and Swarm Intelligence*. ISTE. pp. 189. ISBN 2746215160.
- Zoja Ignatova, Israel Martinez-Perez, Karl-Heinz Zimmermann (January 2008). *DNA Computing Models*^[22]. Springer. pp. 288. ISBN 978-0-387-73635-8. — A new general text to cover the whole field.

External links

- How Stuff Works explanation^[23]
- Physics Web^[24]
- Ars Technica^[25]
- NY Times DNA Computer for detecting Cancer^[26]
- Bringing DNA computers to life, in Scientific American^[27]
- Japanese Researchers store information in bacteria DNA^[28]
- International Meeting on DNA Computing and Molecular Programming^[29]

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Computational epigenetics

Computational epigenetics^{[1] [2]} uses bioinformatic methods to complement experimental research in epigenetics. Due to the recent explosion of epigenome datasets, computational methods play an increasing role in all areas of epigenetic research.

Definition

Research in computational epigenetics comprises the development and application of bioinformatic methods for solving epigenetic questions, as well as computational data analysis and theoretical modeling in the context of epigenetics.

Current research areas

Epigenetic data processing and analysis

Various experimental techniques have been developed for genome-wide mapping of epigenetic information, the most widely used being ChIP-on-chip, ChIP-seq and bisulfite sequencing. All of these methods generate large amounts of data and require efficient ways of data processing and quality control by bioinformatic methods.

Epigenome prediction

A substantial amount of bioinformatic research has been devoted to the prediction of epigenetic information from characteristics of the genome sequence. Such predictions serve a dual purpose. First, accurate epigenome predictions can substitute for experimental data, to some degree, which is particularly relevant for newly discovered epigenetic mechanisms and for species other than human and mouse. Second, prediction algorithms build statistical models of epigenetic information from training data and can therefore act as a first step toward quantitative modeling of an epigenetic mechanism.

Applications in cancer epigenetics

The important role of epigenetic defects for cancer opens up new opportunities for improved diagnosis and therapy. These active areas of research give rise to two questions that are particularly amenable to bioinformatic analysis. First, given a list of genomic regions exhibiting epigenetic differences between tumor cells and controls (or between different disease subtypes), can we detect common patterns or find evidence of a functional relationship of these regions to cancer? Second, can we use bioinformatic methods in order to improve diagnosis and therapy by detecting and classifying important disease subtypes?

Emerging topics

The first wave of research in the field of computational epigenetics was driven by rapid progress of experimental methods for data generation, which required adequate computational methods for data processing and quality control, prompted epigenome prediction studies as a means of understanding the genomic distribution of epigenetic information, and provided the foundation for initial projects on cancer epigenetics. While these topics will continue to be major areas of research and the mere quantity of epigenetic data arising from epigenome projects poses a significant bioinformatic challenge, several additional topics are currently emerging.

- Epigenetic regulatory circuitry: Reverse engineering the regulatory networks that read, write and execute epigenetic codes.

- Population epigenetics: Distilling regulatory mechanisms from the integration of epigenome data with gene expression profiles and haplotype maps for a large sample from a heterogeneous population.
- Evolutionary epigenetics: Learning about epigenome regulation in human (and its medical consequences) by cross-species comparisons.
- Theoretical modeling: Testing our mechanistic and quantitative understanding of epigenetic mechanisms by in silico simulation.
- Statistical genome browsers: Developing a new blend of web services that enable biologists to perform sophisticated genome and epigenome analysis within an easy-to-use genome browser environment.
- Medical epigenetics: Searching for epigenetic mechanisms that play a role in diseases other than cancer, as there is strong circumstantial evidence for epigenetic regulation being involved in mental disorders, autoimmune diseases and other complex diseases.

Epigenetics Databases

1. MethDB [3] Contains information on 19,905 DNA methylation content data and 5,382 methylation patterns for 48 species, 1,511 individuals, 198 tissues and cell lines and 79 phenotypes.
2. PubMeth [4] Contains over 5,000 records on methylated genes in various cancer types.
3. REBASE [5] Contains over 22,000 DNA methyltransferases genes derived from GenBank.
4. MeInfoText [6] Contains gene methylation information across 205 human cancer types.
5. MethPrimerDB [7] Contains 259 primer sets from human, mouse and rat for DNA methylation analysis.
6. The Histone Database [8] Contains 254 sequences from histone H1, 383 from histone H2, 311 from histone H2B, 1043 from histone H3 and 198 from histone H4, altogether representing at least 857 species.
7. ChromDB [9] Contains 9,341 chromatin-associated proteins, including RNAi-associated proteins, for a broad range of organisms.
8. CREMOFAC [10] Contains 1725 redundant and 720 non-redundant chromatin-remodeling factor sequences in eukaryotes.
9. The Krembil Family Epigenetics Laboratory [11] Contains DNA methylation data of human chromosomes 21, 22, male germ cells and DNA methylation profiles in monozygotic and dizygotic twins.
10. MethyLogiX DNA methylation database [12] Contains DNA methylation data of human chromosomes 21 and 22, male germ cells and late-onset Alzheimer's disease.

Sources and further reading

The original version of this article was based on a review paper on computational epigenetics that appeared in the January 2008 issue of the Bioinformatics journal: *Bock, C. and Lengauer, T. (2008) Computational epigenetics. Bioinformatics, 24, 1-10* ^[13]. This review paper provides >100 references to scientific papers and extensive background information. It is published as open access and can be downloaded freely from the publisher's web page: <http://dx.doi.org/10.1093/bioinformatics/btm546> ^[13].

Additional data has been updated and added, based on a review paper on computational epigenetics that appeared in the January 2010 issue of the Bioinformatics ^[14] journal: *Lim S.J., Tan T.W. and Tong, J.C. (2010) Computational epigenetics: the new scientific paradigm. Bioinformatics, 4(7): 331-337* ^[15]. This review paper provides >129 references to scientific papers. It is published as open access and can be downloaded freely from the publisher's web page: <http://bioinformatics.net/004/007000042010.pdf> ^[15].

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- [10] <http://www.jncasr.ac.in/cremofac/>
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Computational biology

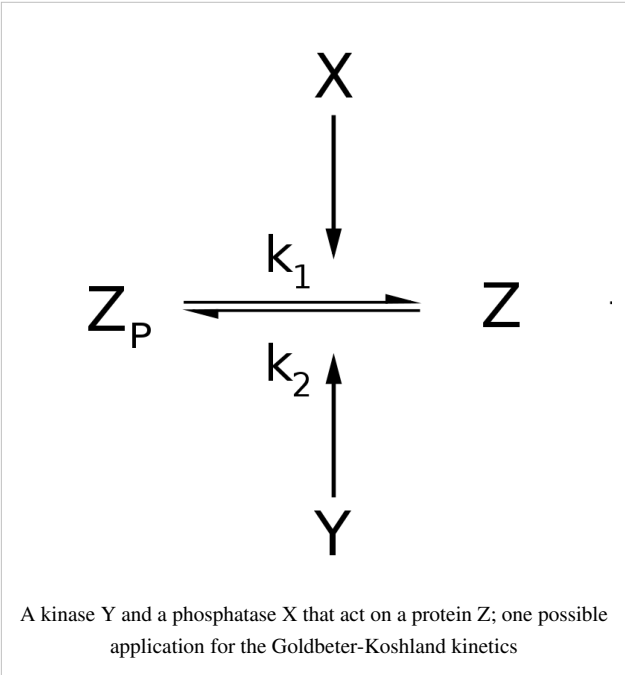
Computational biology is an interdisciplinary field that applies the techniques of computer science, applied mathematics and statistics to address biological problems. The main focus lies on developing mathematical modeling and computational simulation techniques. By these means it addresses scientific research topics with their theoretical and experimental questions without a laboratory. It encompasses the fields of:

- Computational biomodeling, a field concerned with building computer models of biological systems.
 - Bioinformatics, which applies algorithms and statistical techniques to the interpretation, classification and understanding of biological datasets. These typically consist of large numbers of DNA, RNA, or protein sequences. Sequence alignment is used to assemble the datasets for analysis. Comparisons of homologous sequences, gene finding, and prediction of gene expression are the most common techniques used on assembled datasets; however, analysis of such datasets have many applications throughout all fields of biology.
 - Mathematical biology aims at the mathematical representation, treatment and modeling of biological processes, using a variety of applied mathematical techniques and tools.
 - Computational genomics, a field within genomics which studies the genomes of cells and organisms. High-throughput genome sequencing produces lots of data, which requires extensive post-processing (genome assembly) and uses DNA microarray technologies to perform statistical analyses on the genes expressed in individual cell types. This can help find genes of interest for certain diseases or conditions. This field also studies the mathematical foundations of sequencing.
 - Molecular modeling, which consists of modelling the behaviour of molecules of biological importance.
 - Protein structure prediction and structural genomics, which attempt to systematically produce accurate structural models for three-dimensional protein structures that have not been determined experimentally.
 - Computational biochemistry and biophysics, which make extensive use of structural modeling and simulation methods such as molecular dynamics and Monte Carlo method-inspired Boltzmann sampling methods in an attempt to elucidate the kinetics and thermodynamics of protein functions.
-

Goldbeter-Koshland kinetics

The **Goldbeter-Koshland kinetics** describe a steady-state solution for a 2-state biological system. In this system, the interconversion between these two states is performed by two enzymes with opposing effect. One example would be a protein Z that exists in a phosphorylated form Z_p and in an unphosphorylated form Z; the corresponding kinase Y and phosphatase X interconvert the two forms. In this case we would be interested in the equilibrium concentration of the protein Z (Goldbeter-Koshland kinetics only describe equilibrium properties, thus no dynamics can be modeled). It has many applications in the description of biological systems.

The Goldbeter-Koshland kinetics is described by the Goldbeter-Koshland function:



$$z = \frac{[Z]}{[Z]_0} = G(v_1, v_2, J_1, J_2) = \frac{2v_1 J_2}{B + \sqrt{B^2 - 4(v_2 - v_1)v_1 J_2}}$$

with the constants

$$v_1 = k_1[X]; \quad v_2 = k_2[Y]; \quad J_1 = \frac{K_{M1}}{[Z]_0}; \quad J_2 = \frac{K_{M2}}{[Z]_0}; \quad B = v_2 - v_1 + J_1 v_2 + J_2 v_1$$

Graphically the function takes values between 0 and 1 and has a sigmoid behavior. The smaller the parameters J_1 and J_2 the steeper the function gets and the more of a *switch-like* behavior is observed.

Derivation

Since we are looking at equilibrium properties we can write

$$\frac{d[Z]}{dt} \stackrel{!}{=} 0$$

From Michaelis–Menten kinetics we know that the rate at which Z_p is dephosphorylated is $r_1 = \frac{k_1[X][Z_p]}{K_{M1} + [Z_p]}$

and the rate at which Z is phosphorylated is $r_2 = \frac{k_2[Y][Z]}{K_{M2} + [Z]}$. Here the K_M stand for the Michaelis Menten

constant which describes how well the enzymes X and Y bind and catalyze the conversion whereas the kinetic parameters k_1 and k_2 denote the rate constants for the catalyzed reactions. Assuming that the total concentration of Z is constant we can additionally write that $[Z]_0 = [Z_p] + [Z]$ and we thus get:

$$\begin{aligned}
\frac{d[Z]}{dt} = r_1 - r_2 &= \frac{k_1[X]([Z]_0 - [Z])}{K_{M1} + ([Z]_0 - [Z])} - \frac{k_2[Y][Z]}{K_{M2} + [Z]} = 0 \\
&= \frac{k_1[X]([Z]_0 - [Z])}{K_{M1} + ([Z]_0 - [Z])} = \frac{k_2[Y][Z]}{K_{M2} + [Z]} \\
&= \frac{k_1[X](1 - \frac{[Z]}{[Z]_0})}{\frac{K_{M1}}{[Z]_0} + (1 - \frac{[Z]}{[Z]_0})} = \frac{k_2[Y]\frac{[Z]}{[Z]_0}}{\frac{K_{M2}}{[Z]_0} + \frac{[Z]}{[Z]_0}} \\
&= \frac{v_1(1 - z)}{J_1 + (1 - z)} = \frac{v_2 z}{J_2 + z} \quad (1)
\end{aligned}$$

with the constants

$$z = \frac{[Z]}{[Z]_0}; \quad v_1 = k_1[X]; \quad v_2 = k_2[Y]; \quad J_1 = \frac{K_{M1}}{[Z]_0}; \quad J_2 = \frac{K_{M2}}{[Z]_0}; \quad (2)$$

If we thus solve the quadratic equation (1) for z we get:

$$\begin{aligned}
\frac{v_1(1 - z)}{J_1 + (1 - z)} &= \frac{v_2 z}{J_2 + z} \\
J_2 v_1 + z v_1 - J_2 v_1 z - z^2 v_1 &= z v_2 J_1 + v_2 z - z^2 v_2 \\
z^2(v_2 - v_1) - z \underbrace{(v_2 - v_1 + J_1 v_2 + J_2 v_1)}_B + v_1 J_2 &= 0 \\
z &= \frac{B - \sqrt{B^2 - 4(v_2 - v_1)v_1 J_2}}{2(v_2 - v_1)} = \frac{B - \sqrt{B^2 - 4(v_2 - v_1)v_1 J_2}}{2(v_2 - v_1)} \cdot \frac{B + \sqrt{B^2 - 4(v_2 - v_1)v_1 J_2}}{B + \sqrt{B^2 - 4(v_2 - v_1)v_1 J_2}} \\
z &= \frac{4(v_2 - v_1)v_1 J_2}{2(v_2 - v_1)} \cdot \frac{1}{B + \sqrt{B^2 - 4(v_2 - v_1)v_1 J_2}} \\
z &= \frac{2v_1 J_2}{B + \sqrt{B^2 - 4(v_2 - v_1)v_1 J_2}}. \quad (3)
\end{aligned}$$

Thus (3) is a solution to the initial equilibrium problem and describes the equilibrium concentration of $[Z]$ and $[Z_p]$ as a function of the kinetic parameters of the phoshorylation and dephoshorylation reaction and the concentrations of the kinase and phosphatase. The solution is the Goldbeter-Koshland function with the constants from (2):

$$z = \frac{[Z]}{[Z]_0} = G(v_1, v_2, J_1, J_2) = \frac{2v_1 J_2}{B + \sqrt{B^2 - 4(v_2 - v_1)v_1 J_2}}.$$

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Metabolic network

A **metabolic network** is the complete set of metabolic and physical processes that determine the physiological and biochemical properties of a cell. As such, these networks comprise the chemical reactions of metabolism as well as the regulatory interactions that guide these reactions.

With the sequencing of complete genomes, it is now possible to reconstruct the network of biochemical reactions in many organisms, from bacteria to human. Several of these networks are available online: Kyoto Encyclopedia of Genes and Genomes (KEGG)[1], EcoCyc [2] and BioCyc [3]. Metabolic networks are powerful tools, for studying and modelling metabolism. From the study of metabolic networks' topology with graph theory to predictive toxicology and ADME.

See also

- Metabolic network modelling
- Metabolic pathway

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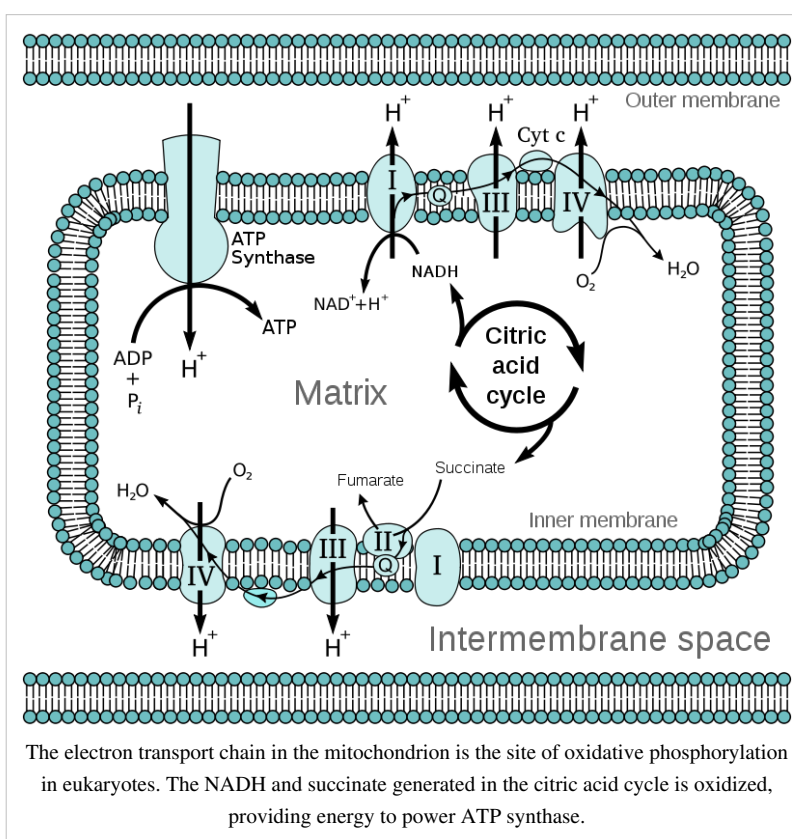
[2] <http://www.ecocyc.org>

[3] <http://biocyc.org>

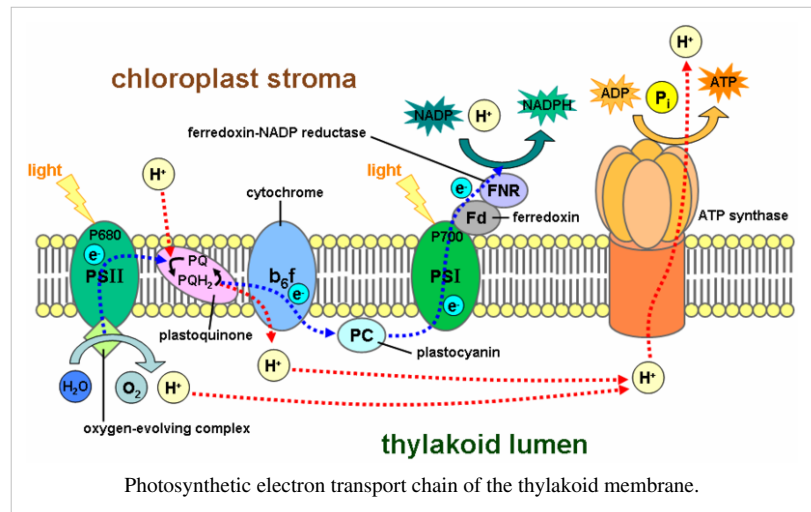
Electron transport chain

An **electron transport chain (ETC)** couples a chemical reaction between an electron donor (such as NADH) and an electron acceptor (such as O_2) to the transfer of H^+ ions across a membrane, through a set of mediating biochemical reactions. These H^+ ions are used to produce adenosine triphosphate (ATP), the main energy intermediate in living organisms, as they move back across the membrane. Electron transport chains are used for extracting energy from sunlight (photosynthesis) and from redox reactions such as the oxidation of sugars (respiration).

In chloroplasts, light drives the conversion of water to oxygen and $NADP^+$ to NADPH and a transfer of H^+ ions. NADPH is used as an electron donor for carbon fixation. In



mitochondria, it is the conversion of oxygen to water, NADH to NAD⁺ and succinate to fumarate that drives the transfer of H⁺ ions. While some bacteria have electron transport chains similar to those in chloroplasts or mitochondria, other bacteria use different electron donors and acceptors. Both the respiratory and photosynthetic electron transport chains are major sites of premature electron leakage to oxygen, thus being major sites of superoxide production and drivers of oxidative stress.



Background

The electron transport chain is also called the **ETC**. An enzyme called ATP synthase catalyzes a reaction to generate ATP. The structure of this enzyme and its underlying genetic code is remarkably conserved in all known forms of life.

ATP synthase is powered by a transmembrane electrochemical gradient in the form of a proton gradient^{[1] [2]}. The function of the electron transport chain is to produce this gradient^{[3] [4]}. In all living organisms, a series of redox reactions is used to produce a transmembrane electrochemical potential gradient.

Redox reactions are chemical reactions in which electrons are transferred from a donor molecule to an acceptor molecule. The underlying force driving these reactions is the Gibbs free energy of the reactants and products. The Gibbs free energy is the energy available ("free") to do work. Any reaction that decreases the overall Gibbs free energy of a system will proceed spontaneously.

The transfer of electrons from a high-energy molecule (the donor) to a lower-energy molecule (the acceptor) can be *spatially* separated into a series of intermediate redox reactions. This is an electron transport chain.

The fact that a reaction is thermodynamically possible does not mean that it will actually occur; for example, a mixture of hydrogen gas and oxygen gas does not spontaneously ignite. It is necessary either to supply an activation energy or to lower the intrinsic activation energy of the system, in order to make most biochemical reactions proceed at a useful rate. Living systems use complex macromolecular structures (enzymes) to lower the activation energies of biochemical reactions.

It is possible to couple a thermodynamically favorable reaction (a transition from a high-energy state to a lower-energy state) to a thermodynamically unfavorable reaction (such as a separation of charges, or the creation of an osmotic gradient), in such a way that the overall free energy of the system decreases (making it thermodynamically possible), while useful work is done at the same time. Biological macromolecules that catalyze a thermodynamically unfavorable reaction *if and only if a thermodynamically favorable reaction occurs simultaneously* underlie all known forms of life.

Electron transport chains capture energy in the form of a transmembrane electrochemical potential gradient. This energy can then be harnessed to do useful work. The gradient can be used to transport molecules across membranes. It can be used to do mechanical work, such as rotating bacterial flagella, and also to produce ATP, a high-energy molecule which can go on to power other cellular reactions.

A small amount of ATP is available from substrate-level phosphorylation (for example, in glycolysis). Some organisms can obtain ATP exclusively by fermentation. In most organisms, however, the majority of ATP is generated by electron transport chains.

Electron transport chains in mitochondria

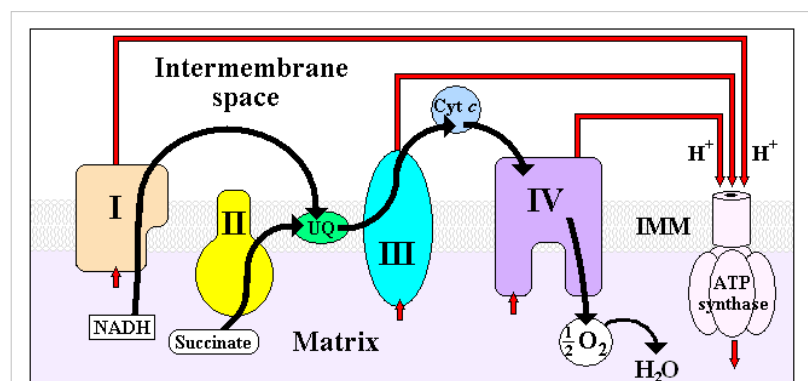
The cells of almost all eukaryotes contain intracellular organelles called mitochondria, which produce ATP. Energy sources such as glucose are initially metabolized in the cytoplasm. The products are imported into mitochondria. Mitochondria continue the process of catabolism using metabolic pathways including the Krebs cycle, fatty acid oxidation, and amino acid oxidation.

The end result of these pathways is the production of two kinds of energy-rich electron donors, NADH and succinate. Electrons from these donors are passed through an electron transport chain to oxygen, which is reduced to water. This is a multi-step redox process that occurs on the mitochondrial inner membrane. The enzymes that catalyze these reactions have the ability to simultaneously create a proton gradient across the membrane, producing a thermodynamically unlikely high-energy state with the potential to do work. Although electron transport occurs with great efficiency, a small percentage of electrons are prematurely leaked to oxygen, resulting in the formation of the toxic free-radical superoxide.

The similarity between intracellular mitochondria and free-living bacteria is striking. The known structural, functional, and DNA similarities between mitochondria and bacteria provide strong evidence that mitochondria evolved from intracellular bacterial symbionts (*see Endosymbiotic theory*).

Mitochondrial redox carriers

Four membrane-bound complexes have been identified in mitochondria. Each is an extremely complex transmembrane structure that is embedded in the inner membrane. Three of them are proton pumps. The structures are electrically connected by lipid-soluble electron carriers and water-soluble electron carriers. The overall electron transport chain



Stylized representation of the ETC. Energy obtained through the transfer of electrons

$\text{NADH} \rightarrow \text{Complex I} \rightarrow \text{Q} \rightarrow \text{Complex III} \rightarrow \text{cytochrome } c \rightarrow \text{Complex IV} \rightarrow \text{O}_2$

Complex II

Complex I

Complex I (NADH dehydrogenase, also called NADH:ubiquinone oxidoreductase; EC 1.6.5.3 [5]) removes two electrons from NADH

and transfers them to a lipid-soluble carrier, *ubiquinone* (Q). The reduced product, *ubiquinol* (QH_2) is free to diffuse within the membrane. At the same time, *Complex I* moves four protons (H^+) across the membrane, producing a proton gradient. Complex I is one of the main sites at which premature electron leakage to oxygen occurs, thus being

one of main sites of production of a harmful free radical called superoxide.

The pathway of electrons occurs as follows:

NADH is oxidized to NAD^+ , reducing Flavin mononucleotide to FMNH_2 in one two-electron step. The next electron carrier is a Fe-S cluster, which can only accept one electron at a time to reduce the ferric ion into a ferrous ion. In a convenient manner, FMNH_2 can be oxidized in only two one-electron steps, through a semiquinone intermediate. The electron thus travels from the FMNH_2 to the Fe-S cluster, then from the Fe-S cluster to the oxidized Q to give the free-radical (semiquinone) form of Q. This happens again to reduce the semiquinone form to the ubiquinol form, QH_2 . During this process, four protons are translocated across the inner mitochondrial membrane, from the matrix to the intermembrane space. This creates a proton gradient that will be later used to generate ATP through oxidative phosphorylation.

Complex II

Complex II (succinate dehydrogenase; EC 1.3.5.1 ^[6]) is not a proton pump. It serves to funnel additional electrons into the quinone pool (Q) by removing electrons from succinate and transferring them (via FAD) to Q. Complex II consists of four protein subunits: SDHA, SDHB, SDHC, and SDHD. Other electron donors (e.g., fatty acids and glycerol 3-phosphate) also funnel electrons into Q (via FAD), again without producing a proton gradient.

Complex III

Complex III (cytochrome bc_1 complex; EC 1.10.2.2 ^[7]) removes in a stepwise fashion two electrons from QH_2 at the Q_O site and sequentially transfers them to two molecules of cytochrome c , a water-soluble electron carrier located within the intermembrane space. The two other electrons are sequentially passed across the protein to the Q_I site where quinone part of ubiquinone is reduced to quinol. A proton gradient is formed because it takes 2 quinol ($4\text{H}+4\text{e}^-$) oxidations at the Q_O site to form one quinol ($2\text{H}+2\text{e}^-$) at the Q_I site. (in total 6 protons: 2 protons reduce quinone to quinol and 4 protons are released from 2 ubiquinol). The bc_1 complex does NOT 'pump' protons, it helps build the proton gradient by an asymmetric absorption/release of protons.

When electron transfer is reduced (by a high membrane potential, point mutations or respiratory inhibitors such as antimycin A), Complex III may leak electrons to molecular oxygen, resulting in the formation of superoxide, a highly-toxic reactive oxygen species, which is thought to contribute to the pathology of a number of diseases and to processes involved in aging.

Complex IV

Complex IV (cytochrome c oxidase; EC 1.9.3.1 ^[8]) removes four electrons from four molecules of cytochrome c and transfers them to molecular oxygen (O_2), producing two molecules of water (H_2O). At the same time, it moves four protons across the membrane, producing a proton gradient. In cyanide poisoning, this enzyme is inhibited.

Coupling with oxidative phosphorylation

The chemiosmotic coupling hypothesis, as proposed by Nobel Prize in Chemistry winner Peter D. Mitchell, explains that the electron transport chain and oxidative phosphorylation are coupled by a proton gradient across the inner mitochondrial membrane. The efflux of protons creates both a pH gradient and an electrochemical gradient. This proton gradient is used by the $\text{F}_\text{O}\text{F}_1$ ATP synthase complex to make ATP via oxidative phosphorylation. ATP synthase is sometimes regarded as *complex V* of the electron transport chain. The F_O component of ATP synthase acts as an ion channel for return of protons back to mitochondrial matrix. During their return, the free energy produced during the generation of the oxidized forms of the electron carriers (NAD^+ and Q) is released. This energy is used to drive ATP synthesis, catalyzed by the F_1 component of the complex.

Coupling with oxidative phosphorylation is a key step for ATP production. However, in certain cases, uncoupling may be biologically useful. The inner mitochondrial membrane of brown adipose tissue contains a large amount of

thermogenin (an uncoupling protein), which acts as uncoupler by forming an alternative pathway for the flow of protons back to matrix. This results in consumption of energy in thermogenesis rather than ATP production. This may be useful in cases when heat production is required, for example in colds or during arise of hibernating animals. Synthetic uncouplers (e.g., 2,4-dinitrophenol) also exist, and, at high doses, are lethal.

Summary

The mitochondrial electron transport chain removes electrons from an electron donor (NADH or QH_2) and passes them to a terminal electron acceptor (O_2) via a series of redox reactions. These reactions are coupled to the creation of a proton gradient across the mitochondrial inner membrane. There are three proton pumps: *I*, *III*, and *IV*. The resulting transmembrane proton gradient is used to make ATP via ATP synthase.

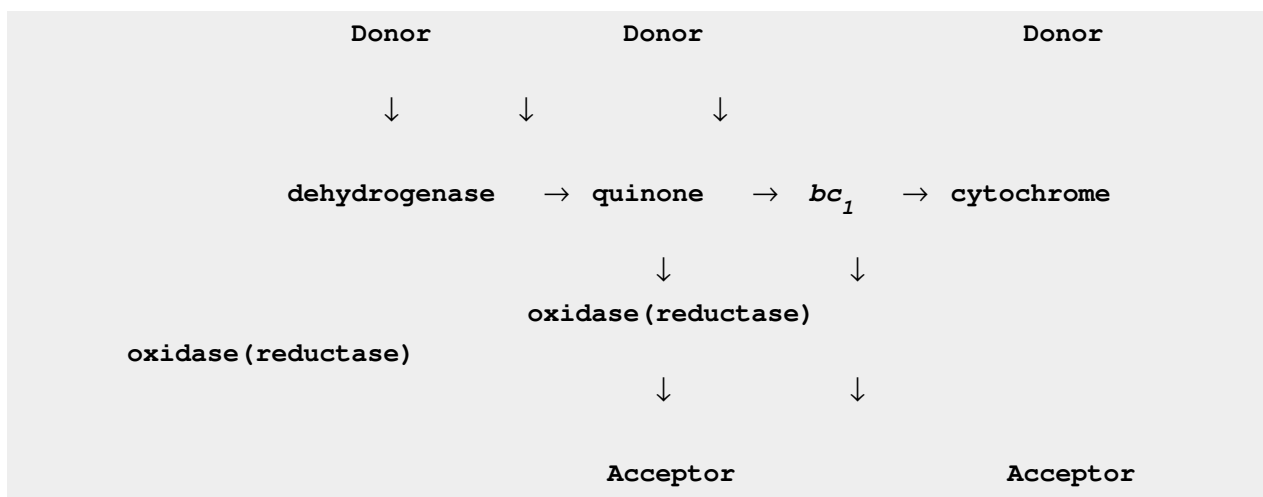
The reactions catalyzed by *Complex I* and *Complex III* exist roughly at equilibrium. This means that these reactions are readily reversible, simply by increasing the concentration of the products relative to the concentration of the reactants (for example, by increasing the proton gradient). ATP synthase is also readily reversible. Thus ATP can be used to make a proton gradient, which in turn can be used to make NADH. This process of **reverse electron transport** is important in many prokaryotic electron transport chains.

Electron transport chains in bacteria

In eukaryotes, NADH is the most important electron donor. The associated electron transport chain is

$\text{NADH} \rightarrow \text{Complex I} \rightarrow \text{Q} \rightarrow \text{Complex III} \rightarrow \text{cytochrome } c \rightarrow \text{Complex IV} \rightarrow \text{O}_2$ where *Complexes I, III* and *IV* are proton pumps, while *Q* and cytochrome *c* are mobile electron carriers. The electron acceptor is molecular oxygen.

In prokaryotes (bacteria and archaea) the situation is more complicated, because there is a number of different electron donors and a number of different electron acceptors. The generalized electron transport chain in bacteria is:



Note that electrons can enter the chain at three levels: at the level of a dehydrogenase, at the level of the quinone pool, or at the level of a mobile cytochrome electron carrier. These levels correspond to successively more positive redox potentials, or to successively decreased potential differences relative to the terminal electron acceptor. In other words, they correspond to successively smaller Gibbs free energy changes for the overall redox reaction $\text{Donor} \rightarrow \text{Acceptor}$.

Individual bacteria use multiple electron transport chains, often simultaneously. Bacteria can use a number of different electron donors, a number of different dehydrogenases, a number of different oxidases and reductases, and a number of different electron acceptors. For example, *E. coli* (when growing aerobically using glucose as an energy source) uses two different NADH dehydrogenases and two different quinol oxidases, for a total of four different electron transport chains operating simultaneously.

A common feature of all electron transport chains is the presence of a proton pump to create a transmembrane proton gradient. Bacterial electron transport chains may contain as many as three proton pumps, like mitochondria, or they may contain only one or two. They always contain at least one proton pump.

Electron donors

In the present day biosphere, the most common electron donors are organic molecules. Organisms that use organic molecules as an energy source are called *organotrophs*. Organotrophs (animals, fungi, protists) and *phototrophs* (plants and algae) constitute the vast majority of all familiar life forms.

Some prokaryotes can use inorganic matter as an energy source. Such organisms are called *lithotrophs* ("rock-eaters"). Inorganic electron donors include hydrogen, carbon monoxide, ammonia, nitrite, sulfur, sulfide, and ferrous iron. Lithotrophs have been found growing in rock formations thousands of meters below the surface of Earth. Because of their volume of distribution, lithotrophs may actually outnumber organotrophs and phototrophs in our biosphere.

The use of inorganic electron donors as an energy source is of particular interest in the study of evolution. This type of metabolism must logically have preceded the use of organic molecules as an energy source.

Dehydrogenases

Bacteria can use a number of different electron donors. When organic matter is the energy source, the donor may be NADH or succinate, in which case electrons enter the electron transport chain via NADH dehydrogenase (similar to *Complex I* in mitochondria) or succinate dehydrogenase (similar to *Complex II*). Other dehydrogenases may be used to process different energy sources: formate dehydrogenase, lactate dehydrogenase, glyceraldehyde-3-phosphate dehydrogenase, H_2 dehydrogenase (hydrogenase), etc. Some dehydrogenases are also proton pumps; others simply funnel electrons into the quinone pool.

Most of dehydrogenases are synthesized only when needed. Depending on the environment in which they find themselves, bacteria select different enzymes from their DNA library and synthesize only those that are needed for growth. Enzymes that are synthesized only when needed are said to be 'inducible'.

Quinone carriers

Quinones are mobile, lipid-soluble carriers that shuttle electrons (and protons) between large, relatively immobile macromolecular complexes embedded in the membrane. Bacteria use *ubiquinone* (the same quinone that mitochondria use) and related quinones such as *menaquinone*.

Proton pumps

A *proton pump* is any process that creates a proton gradient across a membrane. Protons can be physically moved across a membrane; this is seen in mitochondrial *Complexes I* and *IV*. The same effect can be produced by moving electrons in the opposite direction. The result is the disappearance of a proton from the cytoplasm and the appearance of a proton in the periplasm. Mitochondrial *Complex III* uses this second type of proton pump, which is mediated by a quinone (the Q cycle).

Some dehydrogenases are proton pumps; others are not. Most oxidases and reductases are proton pumps, but some are not. Cytochrome bc_1 is a proton pump found in many, but not all, bacteria (it is not found in *E. coli*). As the name implies, bacterial bc_1 is similar to mitochondrial bc_1 (*Complex III*).

Proton pumps are the heart of the electron transport process. They produce the transmembrane electrochemical gradient that supplies energy to the cell.

Cytochrome electron carriers

Cytochromes are pigments that contain iron. They are found in two very different environments.

Some cytochromes are water-soluble carriers that shuttle electrons to and from large, immobile macromolecular structures imbedded in the membrane. The mobile cytochrome electron carrier in mitochondria is cytochrome *c*. Bacteria use a number of different mobile cytochrome electron carriers.

Other cytochromes are found within macromolecules such as *Complex III* and *Complex IV*. They also function as electron carriers, but in a very different, intramolecular, solid-state environment.

Electrons may enter an electron transport chain at the level of a mobile cytochrome or quinone carrier. For example, electrons from inorganic electron donors (nitrite, ferrous iron, etc.) enter the electron transport chain at the cytochrome level. When electrons enter at a redox level greater than NADH, the electron transport chain must operate in reverse to produce this necessary, higher-energy molecule.

Terminal oxidases and reductases

When bacteria grow in aerobic environments, the terminal electron acceptor (O_2) is reduced to water by an enzyme called an *oxidase*. When bacteria grow in anaerobic environments, the terminal electron acceptor is reduced by an enzyme called a *reductase*.

In mitochondria the terminal membrane complex (*Complex IV*) is cytochrome oxidase. Aerobic bacteria use a number of different terminal oxidases. For example, *E. coli* does not have a cytochrome oxidase or a *bc₁* complex. Under aerobic conditions, it uses two different terminal quinol oxidases (both proton pumps) to reduce oxygen to water.

Anaerobic bacteria, which do not use oxygen as a terminal electron acceptor, have terminal reductases individualized to their terminal acceptor. For example, *E. coli* can use fumarate reductase, nitrate reductase, nitrite reductase, DMSO reductase, or trimethylamine-N-oxide reductase, depending on the availability of these acceptors in the environment.

Most terminal oxidases and reductases are *inducible*. They are synthesized by the organism as needed, in response to specific environmental conditions.

Electron acceptors

Just as there are a number of different electron donors (organic matter in organotrophs, inorganic matter in lithotrophs), there are a number of different electron acceptors, both organic and inorganic. If oxygen is available, it is invariably used as the terminal electron acceptor, because it generates the greatest Gibbs free energy change and produces the most energy.

In anaerobic environments, different electron acceptors are used, including nitrate, nitrite, ferric iron, sulfate, carbon dioxide, and small organic molecules such as fumarate.

Since electron transport chains are redox processes, they can be described as the sum of two redox pairs. For example, the mitochondrial electron transport chain can be described as the sum of the $NAD^+/NADH$ redox pair and the O_2/H_2O redox pair. NADH is the electron donor and O_2 is the electron acceptor.

Not every donor-acceptor combination is thermodynamically possible. The redox potential of the acceptor must be more positive than the redox potential of the donor. Furthermore, actual environmental conditions may be far different from *standard* conditions (1 molar concentrations, 1 atm partial pressures, pH = 7), which apply to *standard* redox potentials. For example, hydrogen-evolving bacteria grow at an ambient partial pressure of hydrogen gas of 10^{-4} atm. The associated redox reaction, which is thermodynamically favorable in nature, is thermodynamically impossible under “standard” conditions.

Summary

Bacterial electron transport pathways are, in general, inducible. Depending on their environment, bacteria can synthesize different transmembrane complexes and produce different electron transport chains in their cell membranes. Bacteria select their electron transport chains from a DNA library containing multiple possible dehydrogenases, terminal oxidases and terminal reductases. The situation is often summarized by saying that electron transport chains in bacteria are *branched*, *modular*, and *inducible*.

Photosynthetic electron transport chains

In **oxidative phosphorylation**, electrons are transferred from a high-energy electron donor (e.g., NADH) to an electron acceptor (e.g., O₂) through an electron transport chain. In **photophosphorylation**, the energy of sunlight is used to *create* a high-energy electron donor and an electron acceptor. Electrons are then transferred from the donor to the acceptor through another electron transport chain.

Photosynthetic electron transport chains have many similarities to the oxidative chains discussed above. They use mobile, lipid-soluble carriers (quinones) and mobile, water-soluble carriers (cytochromes, etc.). They also contain a proton pump. It is remarkable that the proton pump in *all* photosynthetic chains resembles mitochondrial *Complex III*.

Photosynthetic electron transport chains are discussed in greater detail in the articles Photophosphorylation, Photosynthesis, Photosynthetic reaction center and Light-dependent reaction.

Summary

Electron transport chains are redox reactions that transfer electrons from an electron donor to an electron acceptor. The transfer of electrons is coupled to the translocation of protons across a membrane, producing a proton gradient. The proton gradient is used to produce useful work.

The coupling of thermodynamically favorable to thermodynamically unfavorable biochemical reactions by biological macromolecules is an example of an **emergent property** – a property that could not have been predicted, even given full knowledge of the primitive geochemical systems from which these macromolecules evolved. It is an open question whether such emergent properties evolve only by chance, or whether they *necessarily* evolve in any large biogeochemical system, given the underlying laws of physics.

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See also

- CoRR Hypothesis
- Hydrogen hypothesis

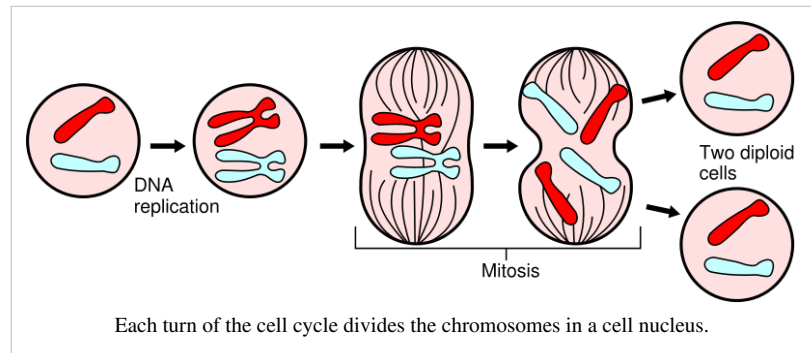
External links

- MeSH *Electron+Transport+Chain+Complex+Proteins* (http://www.nlm.nih.gov/cgi/mesh/2009/MB_cgi?mode=&term=Electron+Transport+Chain+Complex+Proteins)
 - UMich Orientation of Proteins in Membranes *families/superfamily-3* (<http://opm.phar.umich.edu/families.php?superfamily=3>) - Complexes with cytochrome b-like domains
 - UMich Orientation of Proteins in Membranes *families/superfamily-4* (<http://opm.phar.umich.edu/families.php?superfamily=4>) - Bacterial and mitochondrial cytochrome c oxidases
 - UMich Orientation of Proteins in Membranes *families/superfamily-2* (<http://opm.phar.umich.edu/families.php?superfamily=2>) - Photosynthetic reaction centers and photosystems
 - UMich Orientation of Proteins in Membranes *families/superfamily-78* (<http://opm.phar.umich.edu/families.php?superfamily=78>) - Cytochrome c family
 - UMich Orientation of Proteins in Membranes *families/superfamily-101* (<http://opm.phar.umich.edu/families.php?superfamily=101>) - Cupredoxins
 - UMich Orientation of Proteins in Membranes *protein/pdbid-1e6e* (<http://opm.phar.umich.edu/protein.php?pdbid=1e6e>) - Adrenodoxin reductase
 - UMich Orientation of Proteins in Membranes *families/superfamily-130* (<http://opm.phar.umich.edu/families.php?superfamily=130>) - Electron transfer flavoproteins
-

Cell cycle

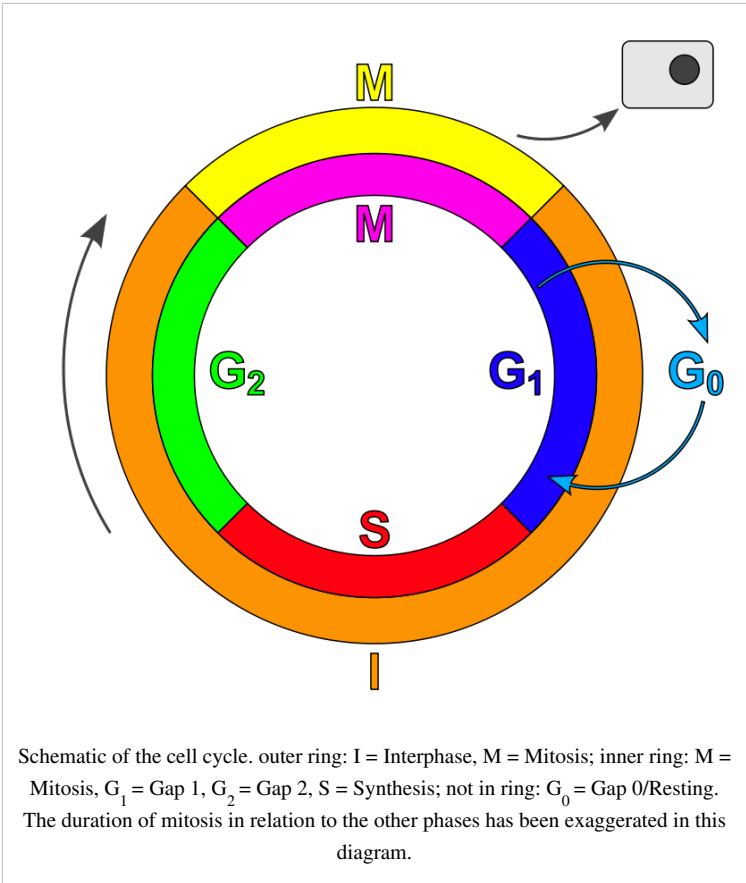
The **cell cycle**, or **cell-division cycle**, is the series of events that takes place in a cell leading to its division and duplication (replication). In cells without a nucleus (prokaryotic), the cell cycle occurs via a process termed binary fission. In cells with a nucleus (eukaryotes), the cell cycle can be divided in two brief periods: interphase—during which the cell

grows, accumulating nutrients needed for mitosis and duplicating its DNA—and the mitosis (M) phase, during which the cell splits itself into two distinct cells, often called "daughter cells". The cell-division cycle is a vital process by which a single-celled fertilized egg develops into a mature organism, as well as the process by which hair, skin, blood cells, and some internal organs are renewed.



Phases

The cell cycle consists of four distinct phases: G_1 phase, S phase (synthesis), G_2 phase (collectively known as interphase) and M phase (mitosis). M phase is itself composed of two tightly coupled processes: mitosis, in which the cell's chromosomes are divided between the two daughter cells, and cytokinesis, in which the cell's cytoplasm divides in half forming distinct cells. Activation of each phase is dependent on the proper progression and completion of the previous one. Cells that have temporarily or reversibly stopped dividing are said to have entered a state of quiescence called G_0 phase.



State	Phase	Abbreviation	Description
quiescent/ senescent	Gap 0	G ₀	A resting phase where the cell has left the cycle and has stopped dividing.
Interphase	Gap 1	G ₁	Cells increase in size in Gap 1. The <i>G₁ checkpoint</i> control mechanism ensures that everything is ready for DNA synthesis.
	Synthesis	S	DNA replication occurs during this phase.
	Gap 2	G ₂	During the gap between DNA synthesis and mitosis, the cell will continue to grow. The <i>G₂ checkpoint</i> control mechanism ensures that everything is ready to enter the M (mitosis) phase and divide.
Cell division	Mitosis	M	Cell growth stops at this stage and cellular energy is focused on the orderly division into two daughter cells. A checkpoint in the middle of mitosis (<i>Metaphase Checkpoint</i>) ensures that the cell is ready to complete cell division.

After cell division, each of the daughter cells begin the interphase of a new cycle. Although the various stages of interphase are not usually morphologically distinguishable, each phase of the cell cycle has a distinct set of specialized biochemical processes that prepare the cell for initiation of cell division.

Resting (G₀ phase)

The term "post-mitotic" is sometimes used to refer to both quiescent and senescent cells. Nonproliferative cells in multicellular eukaryotes generally enter the quiescent G₀ state from G₁ and may remain quiescent for long periods of time, possibly indefinitely (as is often the case for neurons). This is very common for cells that are fully differentiated. Cellular senescence is a state that occurs in response to DNA damage or degradation that would make a cell's progeny nonviable; it is often a biochemical alternative to the self-destruction of such a damaged cell by apoptosis.

Interphase

Before a cell can enter cell division, it needs to take in nutrients. All of the preparations are done during the interphase. Interphase proceeds in three stages, G₁, S, and G₂. Cell division operates in a cycle. Therefore, interphase is preceded by the previous cycle of mitosis and cytokinesis.

G₁ phase

The first phase within interphase, from the end of the previous M phase until the beginning of DNA synthesis is called G₁ (G indicating *gap*). It is also called the growth phase. During this phase the biosynthetic activities of the cell, which had been considerably slowed down during M phase, resume at a high rate. This phase is marked by synthesis of various enzymes that are required in S phase, mainly those needed for DNA replication. Duration of G₁ is highly variable, even among different cells of the same species.^[1]

S phase

The ensuing S phase starts when DNA synthesis commences; when it is complete, all of the chromosomes have been replicated, i.e., each chromosome has two (sister) chromatids. Thus, during this phase, the amount of DNA in the cell has effectively doubled, though the ploidy of the cell remains the same. Rates of RNA transcription and protein synthesis are very low during this phase. An exception to this is histone production, most of which occurs during the S phase.^{[2] [3] [4]}

G₂ phase

The cell then enters the G₂ phase, which lasts until the cell enters mitosis. Again, significant protein synthesis occurs during this phase, mainly involving the production of microtubules, which are required during the process of mitosis. Inhibition of protein synthesis during G₂ phase prevents the cell from undergoing mitosis.

Mitosis (M Phase)

The relatively brief M phase consists of nuclear division (karyokinesis). The M phase has been broken down into several distinct phases, sequentially known as:

- prophase,
- metaphase,
- anaphase, and
- telophase leading to
- cytokinesis (strictly speaking, cytokinesis is not part of mitosis but is an event that directly follows mitosis in which cytoplasm is divided into two daughter cells)

Mitosis is the process in which a eukaryotic cell separates the chromosomes in its cell nucleus into two identical sets in two daughter nuclei.^[5] It is generally followed immediately by cytokinesis, cytoplasm into two daughter cells containing roughly equal shares of these cellular components. Mitosis and cytokinesis together define the **mitotic (M) phase** of the cell cycle - the division of the mother cell into two daughter cells, genetically identical to each other and to their parent cell.

Mitosis occurs exclusively in eukaryotic cells, but occurs in different ways in different species. For example, animals undergo an "open" mitosis, where the nuclear envelope breaks down before the chromosomes separate, while fungi such as *Aspergillus nidulans* and *Saccharomyces cerevisiae* (yeast) undergo a "closed" mitosis, where chromosomes divide within an intact cell nucleus.^[6] Prokaryotic cells, which lack a nucleus, divide by a process called binary fission.

The process of mitosis is complex and highly regulated. The sequence of events is divided into phases, corresponding to the completion of one set of activities and the start of the next. These stages are prophase, prometaphase, metaphase, anaphase and telophase. During the process of mitosis the pairs of chromosomes condense

and attach to fibers that pull the sister chromatids to opposite sides of the cell. The cell then divides in cytokinesis, to produce two identical daughter cells.^[7]

Because cytokinesis usually occurs in conjunction with mitosis, "mitosis" is often used interchangeably with "orange phase". However, there are many cells where mitosis and cytokinesis occur separately, forming single cells with multiple nuclei. This occurs most notably among the fungi and slime moulds, but is found in various different groups. Even in animals, cytokinesis and mitosis may occur independently, for instance during certain stages of fruit fly embryonic development.^[8] Errors in mitosis can either kill a cell through apoptosis or cause mutations that may lead to cancer.

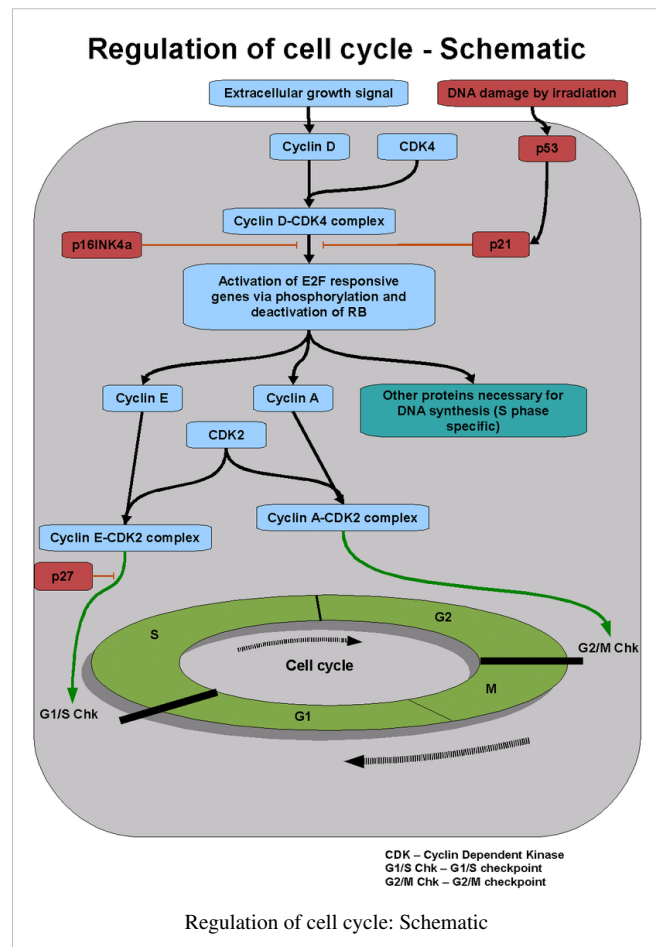
Regulation of eukaryotic cell cycle

Regulation of the cell cycle involves processes crucial to the survival of a cell, including the detection and repair of genetic damage as well as the prevention of uncontrolled cell division. The molecular events that control the cell cycle are ordered and directional; that is, each process occurs in a sequential fashion and it is impossible to "reverse" the cycle.

Role of cyclins and CDKs

Two key classes of regulatory molecules, cyclins and cyclin-dependent kinases (CDKs), determine a cell's progress through the cell cycle.^[9] Leland H. Hartwell, R. Timothy Hunt, and Paul M. Nurse won the 2001 Nobel Prize in Physiology or Medicine for their discovery of these central molecules.^[10] Many of the genes encoding cyclins and CDKs are conserved among all eukaryotes, but in general more complex organisms have more elaborate cell cycle control systems that incorporate more individual components. Many of the relevant genes were first identified by studying yeast, especially *Saccharomyces cerevisiae*;^[11] genetic nomenclature in yeast dubs many these genes *cdc* (for "cell division cycle") followed by an identifying number, e.g., *cdc25* or *cdc20*.

Cyclins form the regulatory subunits and CDKs the catalytic subunits of an activated heterodimer; cyclins have no catalytic activity and CDKs are inactive in the absence of a partner cyclin. When activated by a bound cyclin, CDKs perform a common biochemical reaction called phosphorylation that activates or inactivates target proteins to orchestrate coordinated entry into the next phase of the cell cycle. Different cyclin-CDK combinations determine the downstream proteins targeted. CDKs are constitutively expressed in cells whereas cyclins are synthesised at specific stages of the cell cycle, in response to various molecular signals.^[12]



General mechanism of cyclin-CDK interaction

Upon receiving a pro-mitotic extracellular signal, G_1 cyclin-CDK complexes become active to prepare the cell for S phase, promoting the expression of transcription factors that in turn promote the expression of S cyclins and of enzymes required for DNA replication. The G_1 cyclin-CDK complexes also promote the degradation of molecules that function as S phase inhibitors by targeting them for ubiquitination. Once a protein has been ubiquitinated, it is targeted for proteolytic degradation by the proteasome.

Active S cyclin-CDK complexes phosphorylate proteins that make up the pre-replication complexes assembled during G_1 phase on DNA replication origins. The phosphorylation serves two purposes: to activate each already-assembled pre-replication complex, and to prevent new complexes from forming. This ensures that every portion of the cell's genome will be replicated once and only once. The reason for prevention of gaps in replication is fairly clear, because daughter cells that are missing all or part of crucial genes will die. However, for reasons related to gene copy number effects, possession of extra copies of certain genes would also prove deleterious to the daughter cells.

Mitotic cyclin-CDK complexes, which are synthesized but inactivated during S and G_2 phases, promote the initiation of mitosis by stimulating downstream proteins involved in chromosome condensation and mitotic spindle assembly. A critical complex activated during this process is a ubiquitin ligase known as the anaphase-promoting complex (APC), which promotes degradation of structural proteins associated with the chromosomal kinetochore. APC also targets the mitotic cyclins for degradation, ensuring that telophase and cytokinesis can proceed.

Interphase: Interphase generally lasts at least 12 to 24 hours in mammalian tissue. During this period, the cell is constantly synthesizing RNA, producing protein and growing in size. By studying molecular events in cells, scientists have determined that interphase can be divided into 4 steps: Gap 0 (G_0), Gap 1 (G_1), S (synthesis) phase, Gap 2 (G_2).

Specific action of cyclin-CDK complexes

Cyclin D is the first cyclin produced in the cell cycle, in response to extracellular signals (eg. growth factors). Cyclin D binds to existing CDK4, forming the active cyclin D-CDK4 complex. Cyclin D-CDK4 complex in turn phosphorylates the retinoblastoma susceptibility protein (Rb). The hyperphosphorylated Rb dissociates from the E2F/DP1/Rb complex (which was bound to the E2F responsive genes, effectively "blocking" them from transcription), activating E2F. Activation of E2F results in transcription of various genes like cyclin E, cyclin A, DNA polymerase, thymidine kinase, etc. Cyclin E thus produced binds to CDK2, forming the cyclin E-CDK2 complex, which pushes the cell from G_1 to S phase (G_1 /S transition). Cyclin B along with cdc2 (cdc2 - fission yeasts (CDK1 - mammalia)) forms the cyclin B-cdc2 complex, which initiates the G_2 /M transition.^[13] Cyclin B-cdc2 complex activation causes breakdown of nuclear envelope and initiation of prophase, and subsequently, its deactivation causes the cell to exit mitosis.^[12]

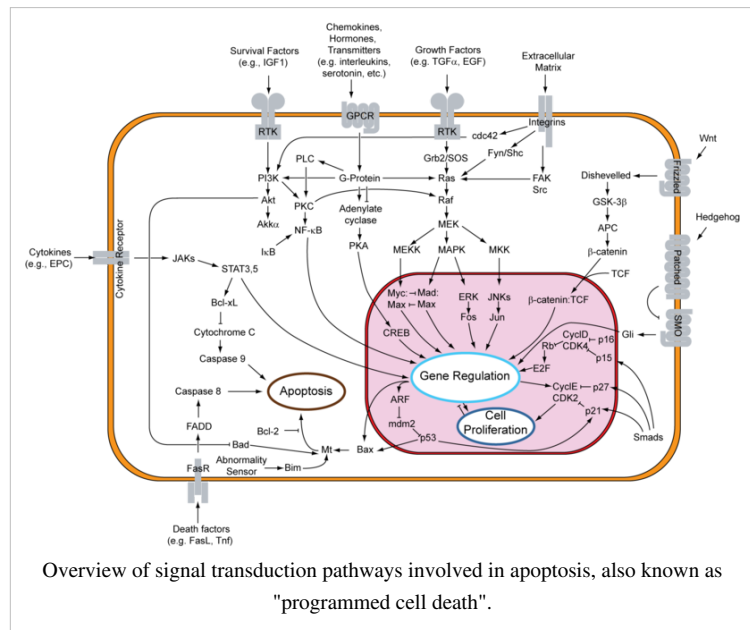
Inhibitors

Two families of genes, the *cip/kip* family and the *INK4a/ARF* (*Inhibitor of Kinase 4/Alternative Reading Frame*) prevent the progression of the cell cycle. Because these genes are instrumental in prevention of tumor formation, they are known as tumor suppressors.

The ***cip/kip* family** includes the genes p21, p27 and p57. They halt cell cycle in G_1 phase, by binding to, and inactivating, cyclin-CDK complexes. p21 is activated by p53 (which, in turn, is triggered by DNA damage eg. due to radiation). p27 is activated by Transforming Growth Factor β (TGF β), a growth inhibitor.

The ***INK4a/ARF* family** includes p16INK4a, which binds to CDK4 and arrests the cell cycle in G_1 phase, and p14arf which prevents p53 degradation.

Synthetic inhibitors of Cdc25 could also be useful for the arrest of cell cycle and therefore be useful as antineoplastic and anticancer agents.^[14]



Checkpoints

Cell cycle checkpoints are used by the cell to monitor and regulate the progress of the cell cycle.^[15] Checkpoints prevent cell cycle progression at specific points, allowing verification of necessary phase processes and repair of DNA damage. The cell cannot proceed to the next phase until checkpoint requirements have been met.

Several checkpoints are designed to ensure that damaged or incomplete DNA is not passed on to daughter cells. Two main checkpoints exist: the G_1/S checkpoint and the G_2/M checkpoint. G_1/S transition is a rate-limiting step in the cell cycle and is also known as restriction point.^[12] An alternative model of the cell cycle response to DNA damage has also been proposed, known as the postreplication checkpoint.

p53 plays an important role in triggering the control mechanisms at both G_1/S and G_2/M checkpoints.

Role in tumor formation

A dysregulation of the cell cycle components may lead to tumor formation. As mentioned above, some genes like the cell cycle inhibitors, RB, p53 etc., when they mutate, may cause the cell to multiply uncontrollably, forming a tumor. Although the duration of cell cycle in tumor cells is equal to or longer than that of normal cell cycle, the proportion of cells that are in active cell division (versus quiescent cells in G_0 phase) in tumors is much higher than that in normal tissue. Thus there is a net increase in cell number as the number of cells that die by apoptosis or senescence remains the same.

The cells which are actively undergoing cell cycle are targeted in cancer therapy as the DNA is relatively exposed during cell division and hence susceptible to damage by drugs or radiation. This fact is made use of in cancer treatment; by a process known as debulking, a significant mass of the tumor is removed which pushes a significant number of the remaining tumor cells from G_0 to G_1 phase (due to increased availability of nutrients, oxygen, growth factors etc.). Radiation or chemotherapy following the debulking procedure kills these cells which have newly entered the cell cycle.^[12]

The fastest cycling mammalian cells in culture, and crypt cells in the intestinal epithelium, have a cycle time as short as 9 to 10 hours. Stem cells in resting mouse skin may have a cycle time of more than 200 hours. Most of this difference is due to the varying length of G_1 , the most variable phase of the cycle. M and S do not vary much.

In general, cells are most radiosensitive in late M and G_2 phases and most resistant in late S.

For cells with a longer cell cycle time and a significantly long G_1 phase, there is a second peak of resistance late in G_1 .

The pattern of resistance and sensitivity correlates with the level of sulfhydryl compounds in the cell. Sulfhydryls are natural radioprotectors and tend to be at their highest levels in S and at their lowest near mitosis.

Synchronization of cell cultures

Several methods can be used to synchronise cell cultures by halting the cell cycle at a particular phase. For example, serum starvation^[16] and treatment with thymidine or aphidicolin^[17] halt the cell in the G_1 phase, mitotic shake-off, treatment with colchicine^[18] and treatment with nocodazole^[19] halt the cell in M phase and treatment with 5-fluorodeoxyuridine halts the cell in S phase.

See also

- Cell cycle mathematical model
- Mitosis
- Meiosis
- Interphase
- Autoradiography -- Used to determine the duration of each phase of the cell cycle.
- Biochemical Switches in the Cell Cycle
- Cdc25

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External links

-  This article incorporates public domain material from the NCBI document "Science Primer"^[20].
 - Transcriptional program of the cell cycle: high-resolution timing^[21]
 - Cell cycle and metabolic cycle regulated transcription in yeast^[22]
 - Cell Cycle Animation^[23] 1Lec.com
 - Cell Cycle and Cytokinesis - The Virtual Library of Biochemistry and Cell Biology^[24]
 - Cell Cycle^[25]
 - Cell Cycle Portal^[26]
 - Fucci:Using GFP to visualize the cell-cycle^[27]
 - Science Creative Quarterly's overview of the cell cycle^[28]
-

- Cells alive ^[29]
- CCO ^[30] The Cell-Cycle Ontology
- KEGG - Human Cell Cycle ^[31]
- Cell cycle modeling ^[32]
- *Drosophila* Cell Cycle Genes - The Interactive Fly ^[33]

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- [23] <http://www.1lec.com/Genetics/Cell%20Cycle/index.html>
- [24] http://www.biochemweb.org/cell_cycle.shtml
- [25] <http://www.landesbioscience.com/journals/cc/index.php>
- [26] <http://www.cellcycles.org>
- [27] <http://www.conncoll.edu/ccacad/zimmer/GFP-ww/cooluses19.html>
- [28] <http://www.scq.ubc.ca/?p=248>

- [29] <http://www.cellsalive.com>
- [30] <http://www.celcycleontology.org>
- [31] <http://www.genome.ad.jp/kegg/pathway/hsa/hsa04110.html>
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Radiobiology

Radiobiology (or *radiation biology*) is the interdisciplinary field of science that studies the biological effects of ionizing and non-ionizing radiation of the whole electromagnetic spectrum, including radioactivity (alpha, beta and gamma), x-rays, ultraviolet radiation, visible light, microwaves, radio wave, low-frequency radiation (such as used in alternate electric transmission, ultrasound thermal radiation (heat), and related modalities. It is a subset of biophysics.

Areas of interest

The interactions between electromagnetic fields (EMF) and organisms can be studied at several levels:

- radiation physics
- radiation chemistry
- molecular and cell biology
- molecular genetics
- cell death and apoptosis
- dose modifying agents
- protection and repair mechanisms
- tissue responses to radiation
- radio-adaptation of living organisms
- high and low-level electromagnetic radiation and health
- specific absorption rates of organisms
- radiation poisoning
- radiation oncology (radiation therapy in cancer)

Radiobiology of non-ionizing radiation includes:

- Bioelectromagnetics
- Magnetobiology

Radiation sources for radiobiology

Radiobiology experiments typically make use of a radiation source which could be:

- An isotopic source, typically ^{137}Cs or ^{60}Co .
 - A particle accelerator generating high energy protons, electrons or charged ions. Biological samples can be irradiated using either a broad, uniform beam or using a microbeam, focused down to cellular or subcellular sizes.
 - A UV lamp.
-

See also

- Radiosensitivity
- Radiology
- Nuclear medicine
- Radioactivity in biology
- Radiophobia
- Cell survival curve
- Relative biological effectiveness
- Health threat from cosmic rays

Notes

- WikiMindMap^[1]

[1] <http://www.wikimindmap.org/viewmap.php?wiki=en.wikipedia.org&topic=radiobiology>

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- The Institute for Radiation Biology at the Helmholtz-Center for Environmental Health (<http://www.helmholtz-muenchen.de/en/isb/isb-home/index.html>)

External links

- The Institute for Radiation Biology at the Helmholtz-Center for Environmental Health (<http://www.helmholtz-muenchen.de/en/isb/isb-home/index.html>)
-

Advanced Experimental Techniques and Methods

2D-FT NMRI and Spectroscopy

2D-FT Nuclear magnetic resonance imaging (2D-FT NMRI), or **two-dimensional Fourier transform** nuclear magnetic resonance imaging (**NMRI**), is primarily a non-invasive imaging technique most commonly used in biomedical research and medical radiology to visualize structures and functions of the living systems and single cells. The physical principle^[1] is essentially the same in N(MRI), nuclear magnetic resonance, FT (NMR) spectroscopy, topical NMR, or even in electron spin resonance (ESR); however, the details are significantly different at present for ESR, as only in the early days of NMR the static magnetic field was scanned for obtaining spectra, as it is still the case in many ESR spectrometers. NMRI, on the other hand, often utilizes a linear magnetic field gradient to obtain an image that combines the visualization of molecular structure and dynamics. It is this dynamic aspect of NMRI, as well as its highest sensitivity for the ^1H nucleus that distinguishes it very dramatically from X-ray CAT scanning that 'misses' hydrogens because of their very low X-ray scattering factor.

Chemical Shifts

NMR is a very useful family of techniques for chemical and biochemical research because of the chemical shift; this effect consists in a frequency shift of the nuclear magnetic resonance for specific chemical groups or atoms as a result of the partial shielding of the corresponding nuclei from the applied, static external magnetic field by the electron orbitals (or molecular orbitals) surrounding such nuclei present in the chemical groups. Thus, the higher the electron density surrounding a specific nucleus the larger the chemical shift will be.

The resulting magnetic field at the nucleus is thus lower than the applied external magnetic field and the resonance frequencies observed as a result of such shielding are lower than the value that would be observed in the absence of any electronic orbital shielding. Furthermore, in order to obtain a chemical shift value independent of the strength of the applied magnetic field and allow for the direct comparison of spectra obtained at different magnetic field values, the chemical shift is defined by the ratio of the strength of the local magnetic field value at the observed (electron orbital-shielded) nucleus by the external magnetic field strength, H_{loc} / H_0 . The first NMR observations of the chemical shift, with the correct physical chemistry interpretation, were reported for ^{19}F containing compounds in the early 1950s by Herbert S. Gutowsky and Charles P. Slichter from the University of Illinois at Urbana (USA).



Advanced 3 T clinical diagnostics and biomedical research NMR Imaging instrument.

A related effect in metals is called the Knight shift, which is due only to the conduction electrons. Such conduction electrons present in metals induce an "additional" local field at the nuclear site, due to the spin re-orientation of the conduction electrons in the presence of the applied (constant), external magnetic field. This is only broadly 'similar' to the chemical shift in either solutions or diamagnetic solids.

Two-dimensional Fourier transform imaging and spectroscopy

2D-FT analysis is a very powerful method for both NMRI and two-dimensional nuclear magnetic resonance spectroscopy (2D-FT NMRS)^[2] that allows the three-dimensional reconstruction of polymer and biopolymer structures at atomic resolution^[3] for molecular weights (Mw) of dissolved biopolymers in aqueous solutions (for example) up to about 50,000 MW. For larger biopolymers or polymers, more complex methods have been developed to obtain limited structural resolution needed for partial 3D-reconstructions of higher molecular structures, e.g. for up 900,000 MW or even oriented microcrystals in aqueous suspensions or single crystals; such methods have also been reported for *in vivo* 2D-FT NMR spectroscopic studies of algae, bacteria, yeast and certain mammalian cells, including human ones.

2D-FT Definition

A 2D-FT, or two-dimensional Fourier transform, transforms a function of two temporal variables into a function of two frequency variables. In MRS the frequencies relate to the resonant frequency offsets caused by chemical shift or J-coupling. In MRI a resonance frequency offset is introduced as a function of position; the frequency variables in the Fourier transformed time-data correspond to spatial location in the final image.^[4]

Example

A 2D Fourier transformation and phase correction is applied to a set of 2D NMR (FID) signals: $s(t_1, t_2)$ yielding a real 2D-FT NMR 'spectrum' (collection of 1D FT-NMR spectra) represented by a matrix $\mathbf{S}$ whose elements are

$$S(\nu_1, \nu_2) = \text{Re} \int \int \cos(\nu_1 t_1) \exp(-i\nu_2 t_2) s(t_1, t_2) dt_1 dt_2$$

where ν_1 and ν_2 denote the discrete indirect double-quantum and single-quantum(detection) axes, respectively, in the 2D NMR experiments. Next, the *covariance matrix* is calculated in the frequency domain according to the following equation

$$\mathbf{C}(\nu'_2, \nu_2) = \mathbf{S}^T \mathbf{S} = \sum_{\nu_1} [S(\nu_1, \nu'_2) S(\nu_1, \nu_2)],$$

with ν_2, ν'_2 taking all possible single-quantum frequency values and with the summation carried out over all discrete, double quantum frequencies ν_1 .

Brief explanation of NMRI diagnostic uses in Pathology

As an example, a diseased tissue such as a malignant tumor, can be detected by 2D-FT NMRI because the hydrogen nuclei of molecules in different tissues return to their equilibrium spin state at different relaxation rates, and also because of the manner in which a malignant tumor spreads and grows rapidly along the blood vessels adjacent to the tumor, also inducing further vascularization to occur. By changing the pulse delays in the RF pulse sequence employed, and/or the RF pulse sequence itself, one may obtain a 'relaxation—based contrast', or contrast enhancement between different types of body tissue, such as normal vs. diseased tissue cells for example.

See also

- Nuclear magnetic resonance (NMR)
- Edward Mills Purcell
- Felix Bloch
- Medical imaging
- Paul C. Lauterbur
- Magnetic resonance microscopy
- Peter Mansfield
- Computed tomography (CT)
- Solid-state NMR
- Knight shift
- John Hasbrouck Van Vleck
- Chemical shift
- Herbert S. Gutowsky
- John S. Waugh
- Charles Pence Slichter
- Protein nuclear magnetic resonance spectroscopy
- Kurt Wüthrich
- Nuclear Overhauser effect
- Fourier transform spectroscopy(FTS)
- Jean Jeneer
- Richard R. Ernst
- FT-NIRS (NIR)
- Magnetic resonance elastography
- Relaxation
- Earth's field NMR (EFNMR)
- Robinson oscillator

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External links

- Cardiac Infarct or "heart attack" Imaged in Real Time by 2D-FT NMRI ^[13]
- Interactive Flash Animation on MRI ^[14] - *Online Magnetic Resonance Imaging physics and technique course*
- Herbert S. Gutowsky
- Jiri Jonas and Charles P. Slichter: NMR Memoires at [[NAS ^[15]] about Herbert Sander Gutowsky; NAS = National Academy of Sciences, USA,]
- 3D Animation Movie about MRI Exam ^[16]
- International Society for Magnetic Resonance in Medicine ^[17]
- Danger of objects flying into the scanner ^[18]

Related Wikipedia websites

- Medical imaging
- Computed tomography
- Magnetic resonance microscopy
- Fourier transform spectroscopy
- FT-NIRS
- Chemical imaging
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- Nuclear magnetic resonance (NMR)
- Chemical shift
- Relaxation
- Robinson oscillator
- Earth's field NMR (EFNMR)
- Rabi cycle

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- [13] http://www.mr-tip.com/exam_gifs/cardiac_infarct_short_axis_cine_6.gif
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- [17] <http://www.ismrm.org>
- [18] http://www.simplyphysics.com/flying_objects.html
- [19] <http://planetphysics.org/encyclopedia/2DFTImaging.html>
- [20] <http://planetphysics.org/>

NMR spectroscopy

Nuclear magnetic resonance spectroscopy, most commonly known as **NMR spectroscopy**, is the name given to a technique which exploits the magnetic properties of certain nuclei. For details regarding this phenomenon and its origins, refer to the nuclear magnetic resonance article. The most important applications for the organic chemist are proton NMR and carbon-13 NMR spectroscopy. In principle, NMR is applicable to any nucleus possessing spin.

Many types of information can be obtained from an NMR spectrum. Much like using infrared spectroscopy (IR) to identify functional groups, analysis of a NMR spectrum provides information on the number and type of chemical entities in a molecule. However, NMR provides much more information than IR.

The impact of NMR spectroscopy on the natural sciences has been substantial. It can, among other things, be used to study mixtures of analytes, to



A 900MHz NMR instrument with a 21.2 T magnet at HWB-NMR, Birmingham, UK

understand dynamic effects such as change in temperature and reaction mechanisms, and is an invaluable tool in understanding protein and nucleic acid structure and function. It can be applied to a wide variety of samples, both in the solution and the solid state.

Basic NMR techniques

When placed in a magnetic field, NMR active nuclei (such as ^1H or ^{13}C) absorb at a frequency characteristic of the isotope. The resonant frequency, energy of the absorption and the intensity of the signal are proportional to the strength of the magnetic field. For example, in a 21 tesla magnetic field, protons resonate at 900 MHz. It is common to refer to a 21 T magnet as a 900 MHz magnet, although different nuclei resonate at a different frequency at this field strength.

In the Earth's magnetic field the same nuclei resonate at audio frequencies. This effect is used in Earth's field NMR spectrometers and other instruments. Because these instruments are portable and inexpensive, they are often used for teaching and field work.

Chemical shift

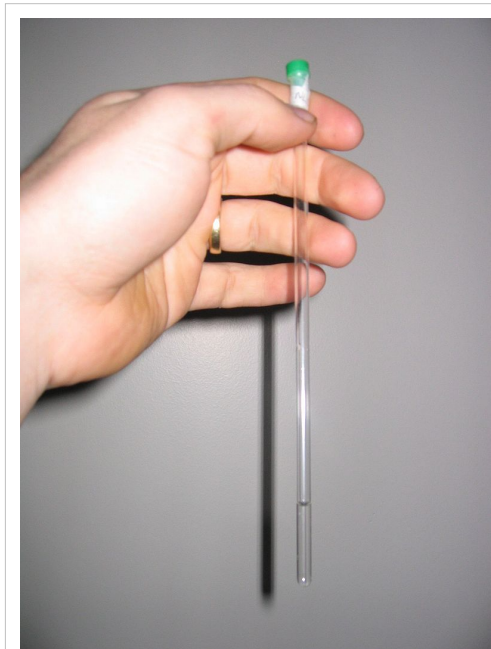
Depending on the local chemical environment, different protons in a molecule resonate at slightly different frequencies. Since both this frequency shift and the fundamental resonant frequency are directly proportional to the strength of the magnetic field, the shift is converted into a *field-independent* dimensionless value known as the chemical shift. The chemical shift is reported as a relative measure from some reference resonance frequency. (For the nuclei ^1H , ^{13}C , and ^{29}Si , TMS (tetramethylsilane) is commonly used as a reference.) This difference between the frequency of the signal and the frequency of the reference is divided by frequency of the reference signal to give the chemical shift. The frequency shifts are extremely small in comparison to the fundamental NMR frequency. A typical frequency shift might be 100 Hz, compared to a fundamental NMR frequency of 100 MHz, so the chemical shift is generally expressed in parts per million (ppm).^[1]

By understanding different chemical environments, the chemical shift can be used to obtain some structural information about the molecule in a sample. The conversion of the raw data to this information is called *assigning* the spectrum. For example, for the ^1H -NMR spectrum for ethanol ($\text{CH}_3\text{CH}_2\text{OH}$), one would expect three specific signals at three specific chemical shifts: one for the CH_3 group, one for the CH_2 group and one for the OH group. A typical CH_3 group has a shift around 1 ppm, a CH_2 attached to an OH has a shift of around 4 ppm and an OH has a shift around 2–3 ppm depending on the solvent used.

Because of molecular motion at room temperature, the three methyl protons *average* out during the course of the NMR experiment (which typically requires a few ms). These protons become degenerate and form a peak at the same chemical shift.

The shape and size of peaks are indicators of chemical structure too. In the example above—the proton spectrum of ethanol—the CH_3 peak would be three times as large as the OH. Similarly the CH_2 peak would be twice the size of the OH peak but only 2/3 the size of the CH_3 peak.

Modern analysis software allows analysis of the size of peaks to understand how many protons give rise to the peak. This is known as integration—a mathematical process which calculates the area under a graph (essentially what a



The NMR sample is prepared in a thin-walled glass tube - an NMR tube.

spectrum is). The analyst must integrate the peak and not measure its height because the peaks also have *width*—and thus its size is dependent on its area not its height. However, it should be mentioned that the number of protons, or any other observed nucleus, is only proportional to the intensity, or the integral, of the NMR signal, in the very simplest one-dimensional NMR experiments. In more elaborate experiments, for instance, experiments typically used to obtain carbon-13 NMR spectra, the integral of the signals depends on the relaxation rate of the nucleus, and its scalar and dipolar coupling constants. Very often these factors are poorly understood - therefore, the integral of the NMR signal is very difficult to interpret in more complicated NMR experiments.

J-coupling

Multiplicity	Intensity Ratio
Singlet (s)	1
Doublet (d)	1:1
Triplet (t)	1:2:1
Quartet (q)	1:3:3:1
Quintet	1:4:6:4:1
Sextet	1:5:10:10:5:1
Septet	1:6:15:20:15:6:1

Some of the most useful information for structure determination in a one-dimensional NMR spectrum comes from **J-coupling** or **scalar coupling** (a special case of spin-spin coupling) between NMR active nuclei. This coupling arises from the interaction of different spin states through the chemical bonds of a molecule and results in the splitting of NMR signals. These splitting patterns can be complex or simple and, likewise, can be straightforwardly interpretable or deceptive. This coupling provides detailed insight into the connectivity of atoms in a molecule.

Coupling to n equivalent (spin $\frac{1}{2}$) nuclei splits the signal into a $n+1$ **multiplet** with intensity ratios following Pascal's triangle as described on the right. Coupling to additional spins will lead to further splittings of each component of the multiplet e.g. coupling to two different spin $\frac{1}{2}$ nuclei with significantly different coupling constants will lead to a *doublet of doublets* (abbreviation: dd). Note that coupling between nuclei that are chemically equivalent (that is, have the same chemical shift) has no effect on the NMR spectra and couplings between nuclei that are distant (usually more than 3 bonds apart for protons in flexible molecules) are usually too small to cause observable splittings. *Long-range* couplings over more than three bonds can often be observed in cyclic and aromatic compounds, leading to more complex splitting patterns.

For example, in the proton spectrum for ethanol described above, the CH_3 group is split into a *triplet* with an intensity ratio of 1:2:1 by the two neighboring CH_2 protons. Similarly, the CH_2 is split into a *quartet* with an intensity ratio of 1:3:3:1 by the three neighboring CH_3 protons. In principle, the two CH_2 protons would also be split again into a *doublet* to form a *doublet of quartets* by the hydroxyl proton, but intermolecular exchange of the acidic hydroxyl proton often results in a loss of coupling information.

Coupling to any spin $\frac{1}{2}$ nuclei such as phosphorus-31 or fluorine-19 works in this fashion (although the magnitudes of the coupling constants may be very different). But the splitting patterns differ from those described above for nuclei with spin greater than $\frac{1}{2}$ because the spin quantum number has more than two possible values. For instance, coupling to deuterium (a spin 1 nucleus) splits the signal into a *1:1:1 triplet* because the spin 1 has three spin states. Similarly, a spin $\frac{3}{2}$ nucleus splits a signal into a *1:1:1:1 quartet* and so on.

Coupling combined with the chemical shift (and the integration for protons) tells us not only about the chemical environment of the nuclei, but also the number of *neighboring* NMR active nuclei within the molecule. In more complex spectra with multiple peaks at similar chemical shifts or in spectra of nuclei other than hydrogen, coupling

is often the only way to distinguish different nuclei.

Second-order (or strong) coupling

The above description assumes that the coupling constant is small in comparison with the difference in NMR frequencies between the inequivalent spins. If the shift separation decreases (or the coupling strength increases), the multiplet intensity patterns are first distorted, and then become more complex and less easily analyzed (especially if more than two spins are involved). Intensification of some peaks in a multiplet is achieved at the expense of the remainder, which sometimes almost disappear in the background noise, although the integrated area under the peaks remains constant. In most high-field NMR, however, the distortions are usually modest and the characteristic distortions (*roofing*) can in fact help to identify related peaks.

Second-order effects decrease as the frequency difference between multiplets increases, so that high-field (i.e. high-frequency) NMR spectra display less distortion than lower frequency spectra. Early spectra at 60 MHz were more prone to distortion than spectra from later machines typically operating at frequencies at 200 MHz or above.

Magnetic inequivalence

More subtle effects can occur if chemically equivalent spins (i.e. nuclei related by symmetry and so having the same NMR frequency) have different coupling relationships to external spins. Spins that are chemically equivalent but are not indistinguishable (based on their coupling relationships) are termed magnetically inequivalent. For example, the 4 H sites of 1,2-dichlorobenzene divide into two chemically equivalent pairs by symmetry, but an individual member of one of the pairs has different couplings to the spins making up the other pair. Magnetic inequivalence can lead to highly complex spectra which can only be analyzed by computational modeling. Such effects are more common in NMR spectra of aromatic and other non-flexible systems, while conformational averaging about C-C bonds in flexible molecules tends to equalize the couplings between protons on adjacent carbons, reducing problems with magnetic inequivalence.

Correlation spectroscopy

Correlation spectroscopy is one of several types of two-dimensional nuclear magnetic resonance (NMR) spectroscopy. This type of NMR experiment is best known by its acronym, COSY. Other types of two-dimensional NMR include J-spectroscopy, exchange spectroscopy (EXSY), Nuclear Overhauser effect spectroscopy (NOESY), total correlation spectroscopy (TOCSY) and heteronuclear correlation experiments, such as HSQC, HMQC, and HMBC. Two-dimensional NMR spectra provide more information about a molecule than one-dimensional NMR spectra and are especially useful in determining the structure of a molecule, particularly for molecules that are too complicated to work with using one-dimensional NMR. The first two-dimensional experiment, COSY, was proposed by Jean Jeener, a professor at Université Libre de Bruxelles, in 1971. This experiment was later implemented by Walter P. Aue, Enrico Bartholdi and Richard R. Ernst, who published their work in 1976.^[2]

Solid-state nuclear magnetic resonance

A variety of physical circumstances does not allow molecules to be studied in solution, and at the same time not by other spectroscopic techniques to an atomic level, either. In solid-phase media, such as crystals, microcrystalline powders, gels, anisotropic solutions, etc., it is in particular the dipolar coupling and chemical shift anisotropy that become dominant to the behaviour of the nuclear spin systems. In conventional solution-state NMR spectroscopy, these additional interactions would lead to a significant broadening of spectral lines. A variety of techniques allows to establish high-resolution conditions, that can, at least for ^{13}C spectra, be comparable to solution-state NMR spectra.

Two important concepts for high-resolution solid-state NMR spectroscopy are the limitation of possible molecular orientation by sample orientation, and the reduction of anisotropic nuclear magnetic interactions by sample spinning.

Of the latter approach, fast spinning around the magic angle is a very prominent method, when the system comprises spin $1/2$ nuclei. A number of intermediate techniques, with samples of partial alignment or reduced mobility, is currently being used in NMR spectroscopy.

Applications in which solid-state NMR effects occur are often related to structure investigations on membrane proteins, protein fibrils or all kinds of polymers, and chemical analysis in inorganic chemistry, but also include "exotic" applications like the plant leaves and fuel cells.

NMR spectroscopy applied to proteins

Much of the recent innovation within NMR spectroscopy has been within the field of protein NMR, which has become a very important technique in structural biology. One common goal of these investigations is to obtain high resolution 3-dimensional structures of the protein, similar to what can be achieved by X-ray crystallography. In contrast to X-ray crystallography, NMR is primarily limited to relatively small proteins, usually smaller than 35 kDa, though technical advances allow ever larger structures to be solved. NMR spectroscopy is often the only way to obtain high resolution information on partially or wholly intrinsically unstructured proteins. It is now a common tool for the determination of Conformation Activity Relationships where the structure before and after interaction with, for example, a drug candidate is compared to its known biochemical activity.

Proteins are orders of magnitude larger than the small organic molecules discussed earlier in this article, but the same NMR theory applies. Because of the increased number of each element present in the molecule, the basic 1D spectra become crowded with overlapping signals to an extent where analysis is impossible. Therefore, multidimensional (2, 3 or 4D) experiments have been devised to deal with this problem. To facilitate these experiments, it is desirable to isotopically label the protein with ^{13}C and ^{15}N because the predominant naturally occurring isotope ^{12}C is not NMR-active, whereas the nuclear quadrupole moment of the predominant naturally occurring ^{14}N isotope prevents high resolution information to be obtained from this nitrogen isotope. The most important method used for structure determination of proteins utilizes NOE experiments to measure distances between pairs of atoms within the molecule. Subsequently, the obtained distances are used to generate a 3D structure of the molecule using a computer program.

See also

- In vivo magnetic resonance spectroscopy
 - Low field NMR
 - Magnetic Resonance Imaging
 - Nuclear Magnetic Resonance
 - NMR spectra database
 - NMR tube - includes a section on sample preparation
 - Protein nuclear magnetic resonance spectroscopy
 - NMR spectroscopy of stereoisomers
-

External links

- Protein NMR- A Practical Guide ^[3] Practical guide to NMR, in particular protein NMR assignment
- James Keeler. "Understanding NMR Spectroscopy" ^[4] (reprinted at University of Cambridge). University of California, Irvine. Retrieved 2007-05-11.
- The Basics of NMR ^[5] - A non-technical overview of NMR theory, equipment, and techniques by Dr. Joseph Hornak, Professor of Chemistry at RIT
- NMRWiki.ORG ^[6] project, a Wiki dedicated to NMR, MRI, and EPR.
- NMR spectroscopy for organic chemistry ^[7]
- The Spectral Game ^[8] NMR spectroscopy game.
- Spectra library ^[9] NMR spectroscopy library

Free NMR processing, analysis and simulation software

- WINDNMR-Pro ^[10] - simulation software for interactive calculation of first and second-order spin-coupled multiplets and a variety of DNMR lineshapes.
- CARA ^[11] - resonance assignment software developed at the Wüthrich group
- NMRShiftDB ^[12] - open database and NMR prediction website
- Spinworks ^[13]
- SPINUS ^[14] website that uses neural networks to predict NMR spectra from chemical structures

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- [4] <http://www-keeler.ch.cam.ac.uk/lectures/Irvine/>
- [5] <http://www.cis.rit.edu/htbooks/nmr/>
- [6] <http://nmrwiki.org>
- [7] <http://www.organicworldwide.net/nmr.html>
- [8] <http://spectralgame.com>
- [9] <http://nmr.chinanmr.cn/guide/eNMR/eNMRindex.html>
- [10] <http://www.chem.wisc.edu/areas/reich/plt/windnmr.htm>
- [11] <http://cara.nmr.ch>
- [12] <http://www.nmrshiftdb.org>
- [13] <http://www.umanitoba.ca/chemistry/nmr/spinworks/>
- [14] <http://www2.chemie.uni-erlangen.de/services/spinus/>

Fourier transform spectroscopy

Fourier transform spectroscopy is a measurement technique whereby spectra are collected based on measurements of the coherence of a radiative source, using time-domain or space-domain measurements of the electromagnetic radiation or other type of radiation. It can be applied to a variety of types of spectroscopy including optical spectroscopy, infrared spectroscopy (FT IR, FT-NIRS), Fourier transform (FT) nuclear magnetic resonance^[1], mass spectrometry and electron spin resonance spectroscopy. There are several methods for measuring the temporal coherence of the light, including the continuous wave *Michelson* or *Fourier transform* spectrometer and the pulsed Fourier transform spectrograph (which is more sensitive and has a much shorter sampling time than conventional spectroscopic techniques, but is only applicable in a laboratory environment).

Conceptual introduction

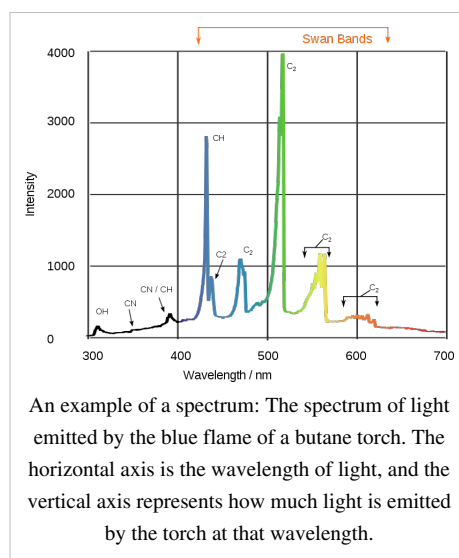
Measuring an emission spectrum

One of the most basic tasks in spectroscopy is to characterize the spectrum of a light source: How much light is emitted at each different wavelength. The most straightforward way to measure a spectrum is to pass the light through a monochromator, an instrument that blocks all of the light *except* the light at a certain wavelength (the un-blocked wavelength is set by a knob on the monochromator). Then the intensity of this remaining (single-wavelength) light is measured. The measured intensity directly indicates how much light is emitted at that wavelength. By varying the monochromator's wavelength setting, the full spectrum can be measured. This simple scheme in fact describes how *some* spectrometers work.

Fourier transform spectroscopy is a less intuitive way to get the same information. Rather than allowing only one wavelength at a time to pass through to the detector, this technique lets through a beam containing many different wavelengths of light at once, and measures the *total* beam intensity. Next, the beam is modified to contain a *different* combination of wavelengths, giving a second data point. This process is repeated many times. Afterwards, a computer takes all this data and works backwards to infer how much light there is at each wavelength.

To be more specific, between the light source and the detector, there is a certain configuration of mirrors that allows some wavelengths to pass through but blocks others (due to wave interference). The beam is modified for each new data point by moving one of the mirrors; this changes the set of wavelengths that can pass through.

As mentioned, computer processing is required to turn the raw data (light intensity for each mirror position) into the desired result (light intensity for each wavelength). The processing required turns out to be a common algorithm called the Fourier transform (hence the name, "Fourier transform spectroscopy"). The raw data is sometimes called an "interferogram".



An example of a spectrum: The spectrum of light emitted by the blue flame of a butane torch. The horizontal axis is the wavelength of light, and the vertical axis represents how much light is emitted by the torch at that wavelength.

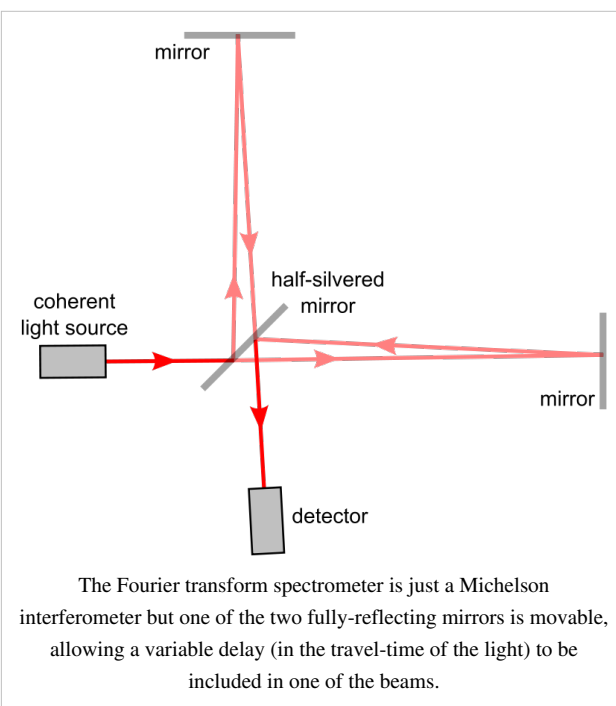
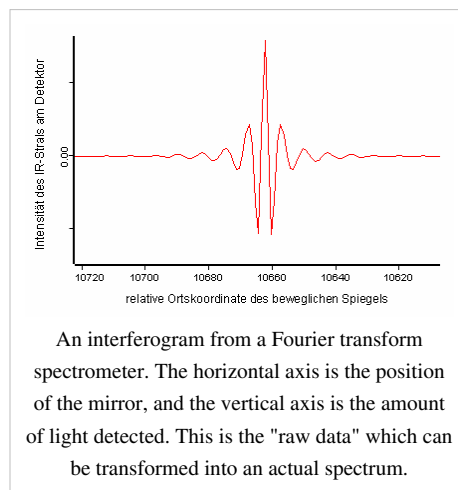
Measuring an absorption spectrum

The method of Fourier transform spectroscopy can also be used for absorption spectroscopy. The primary example is "FTIR Spectroscopy", a common technique in chemistry. In general, the goal of absorption spectroscopy is to measure how well a sample absorbs or transmits light at each different wavelength. However, any technique for *emission* spectroscopy can also be used for *absorption* spectroscopy as follows: Assume you have a working spectrometer that can measure the spectrum of any light source shining into it (as described above). Shine a broadband light source into the spectrometer, then shine the same light source *through the sample* into the same spectrometer. Comparing the two spectra, it will be obvious which wavelengths get absorbed by the sample and which wavelengths can pass right through the sample. (More precisely, the spectrum with the sample, divided by the "background" spectrum without the sample, equals the fraction of light that the sample can transmit at each wavelength.)

Accordingly, the technique of "Fourier transform spectroscopy" can be used both for measuring emission spectra (for example, the emission spectrum of a star), *and* absorption spectra (for example, the absorption spectrum of a glass of liquid).

Continuous wave *Michelson* or *Fourier transform* spectrograph

The Michelson spectrograph is similar to the instrument used in the Michelson-Morley experiment. Light from the source is split into two beams by a half-silvered mirror, one is reflected off a fixed mirror and one off a moving mirror which introduces a time delay -- the Fourier transform spectrometer is just a Michelson interferometer with a movable mirror. The beams interfere, allowing the temporal coherence of the light to be measured at each different time delay setting, effectively converting the time domain into a spatial coordinate. By making measurements of the signal at many discrete positions of the moving mirror, the spectrum can be reconstructed using a Fourier transform of the temporal coherence of the light. Michelson spectrographs are capable of very high spectral resolution observations of very bright sources. The Michelson or Fourier transform spectrograph was popular for infra-red applications at a time when infra-red astronomy only had single pixel detectors. Imaging Michelson spectrometers are a possibility, but in general have been supplanted by imaging Fabry-Perot instruments which are easier to construct.



Extracting the spectrum

The intensity as a function of the path length difference in the interferometer p and wavenumber $\tilde{\nu} = 1/\lambda$ is ^[2]

$$I(p, \tilde{\nu}) = I(\tilde{\nu})[1 + \cos(2\pi\tilde{\nu}p)],$$

where $I(\tilde{\nu})$ is the spectrum to be determined. Note that it is not necessary for $I(\tilde{\nu})$ to be modulated by the sample before the interferometer. In fact, most FTIR spectrometers place the sample after the interferometer in the optical path. The total intensity at the detector is

$$I(p) = \int_0^\infty I(p, \tilde{\nu}) d\tilde{\nu} = \int_0^\infty I(\tilde{\nu})[1 + \cos(2\pi\tilde{\nu}p)] d\tilde{\nu}.$$

This is just a Fourier cosine transform. The inverse gives us our desired result in terms of the measured quantity $I(p)$:

$$I(\tilde{\nu}) = 4 \int_0^\infty [I(p) - \frac{1}{2}I(p=0)] \cos(2\pi\tilde{\nu}p) dp.$$

Pulsed Fourier transform spectrometer

A pulsed *Fourier transform* spectrometer does not employ transmittance techniques. In the most general description of pulsed FT spectrometry, a sample is exposed to an energizing event which causes a periodic response. The frequency of the periodic response, as governed by the field conditions in the spectrometer, is indicative of the measured properties of the analyte.

Examples of Pulsed Fourier transform spectrometry

In magnetic spectroscopy (EPR, NMR), an RF pulse in a strong ambient magnetic field is used as the energizing event. This turns the magnetic particles at an angle to the ambient field, resulting in gyration. The gyrating spins then induce a periodic current in a detector coil. Each spin exhibits a characteristic frequency of gyration (relative to the field strength) which reveals information about the analyte.

In FT-mass spectrometry, the energizing event is the injection of the charged sample into the strong electromagnetic field of a cyclotron. These particles travel in circles, inducing a current in a fixed coil on one point in their circle. Each traveling particle exhibits a characteristic cyclotron frequency-field ratio revealing the masses in the sample.

The Free Induction Decay

Pulsed FT spectrometry gives the advantage of requiring a single, time-dependent measurement which can easily deconvolute a set of similar but distinct signals. The resulting composite signal, is called a *free induction decay*, because typically the signal will decay due to inhomogeneities in sample frequency, or simply unrecoverable loss of signal due to entropic loss of the property being measured.

Fellgett Advantage

One of the most important advantages of Fourier transform spectroscopy was shown by P.B. Fellgett, an early advocate of the method. The Fellgett advantage, also known as the multiplex principle, states that a multiplex spectrometer such as the Fourier transform spectroscopy will produce a gain of the order of the square root of m in the signal-to-noise ratio of the resulting spectrum, when compared with an equivalent scanning monochromator, where m is the number of elements comprising the resulting spectrum when the measurement noise is dominated by detector noise.

Converting spectra from time domain to frequency domain

$$S(t) = \int_{-\infty}^{\infty} I(\nu) e^{-i\nu 2\pi t} d\nu$$

The sum is performed over all contributing frequencies to give a signal $S(t)$ in the time domain.

$$I(\nu) = \int_{-\infty}^{\infty} S(t) e^{i\nu 2\pi t} dt$$

gives non-zero value when $S(t)$ contains a component that matches the oscillating function.

Remember that

$$e^{ix} = \cos x + i \sin x$$

See also

- Applied spectroscopy
- 2D-FT NMRI and Spectroscopy
- Forensic chemistry
- Forensic polymer engineering
- nuclear magnetic resonance
- Infra-red spectroscopy

Further reading

- Ellis, D.I. and Goodacre, R. (2006). "Metabolic fingerprinting in disease diagnosis: biomedical applications of infrared and Raman spectroscopy". *The Analyst* **131**: 875–885. doi:10.1039/b602376m.

External links

- Description of how a Fourier transform spectrometer works ^[3]
- The Michelson or Fourier transform spectrograph ^[4]
- Internet Journal of Vibrational Spectroscopy - How FTIR works ^[5]
- Fourier Transform Spectroscopy Topical Meeting and Tabletop Exhibit ^[6]

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- [3] <http://scienceworld.wolfram.com/physics/FourierTransformSpectrometer.html>
- [4] <http://www.astro.livjm.ac.uk/courses/phys362/notes/>
- [5] <http://www.ijvs.com/volume5/edition5/section1.html#Feature>
- [6] <http://www.osa.org/meetings/topicalmeetings/fts/default.aspx>

Neuroimaging

Neuroimaging includes the use of various techniques to either directly or indirectly image the structure, function/pharmacology of the brain. It is a relatively new discipline within medicine and neuroscience/psychology.^[1]

Overview

Neuroimaging falls into two broad categories:

- Structural imaging, which deals with the structure of the brain and the diagnosis of gross (large scale) intracranial disease (such as tumor), and injury, and
- functional imaging, which is used to diagnose metabolic diseases and lesions on a finer scale (such as Alzheimer's disease) and also for neurological and cognitive psychology research and building brain-computer interfaces.

Functional imaging enables, for example, the processing of information by centers in the brain to be visualized directly. Such processing causes the involved area of the brain to increase metabolism and "light up" on the scan.

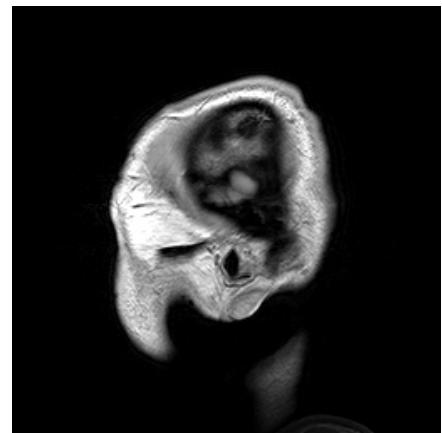
History

In 1918 the American neurosurgeon Walter Dandy introduced the technique of ventriculography. X-ray images of the ventricular system within the brain were obtained by injection of filtered air directly into one or both lateral ventricles of the brain. Dandy also observed that air introduced into the subarachnoid space via lumbar spinal puncture could enter the cerebral ventricles and also demonstrate the cerebrospinal fluid compartments around the base of the brain and over its surface. This technique was called pneumoencephalography.

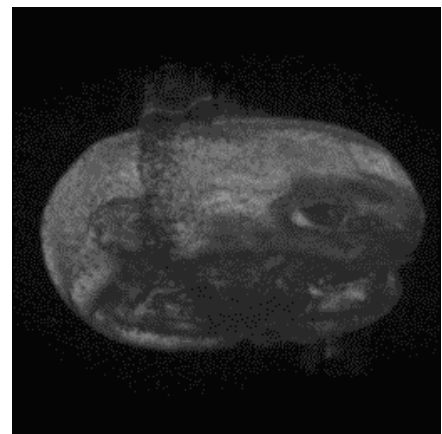
In 1927 Egas Moniz introduced cerebral angiography, whereby both normal and abnormal blood vessels in and around the brain could be visualized with great precision.

In the early 1970s, Allan McLeod Cormack and Godfrey Newbold Hounsfield introduced computerized axial tomography (CAT or CT scanning), and ever more detailed anatomic images of the brain became available for diagnostic and research purposes. Cormack and Hounsfield won the 1979 Nobel Prize for Physiology or Medicine for their work. Soon after the introduction of CAT in the early 1980s, the development of radioligands allowed single photon emission computed tomography (SPECT) and positron emission tomography (PET) of the brain.

More or less concurrently, magnetic resonance imaging (MRI or MR scanning) was developed by researchers including Peter Mansfield and Paul Lauterbur, who were awarded the Nobel Prize for Physiology or Medicine in 2003. In the early 1980s MRI was introduced clinically, and during the 1980s a veritable explosion of technical refinements and diagnostic MR applications took place. Scientists soon learned that the large blood flow changes measured by PET could also be imaged by the correct type of MRI. Functional magnetic resonance imaging (fMRI) was born, and since the 1990s, fMRI has come to dominate the brain mapping field due to its low invasiveness, lack of radiation exposure, and relatively wide availability. As noted above fMRI is also beginning to dominate the field



Para-sagittal MRI of the head in a patient with benign familial macrocephaly.



3-D MRI of a section of the head.

of stroke treatment.

In early 2000s the field of neuroimaging reached the stage where limited practical applications of functional brain imaging have become feasible. The main application area is crude forms of brain-computer interface.

Brain imaging techniques

Computed axial tomography

Computed tomography (CT) or *Computed Axial Tomography* (CAT) scanning uses a series of x-rays of the head taken from many different directions. Typically used for quickly viewing brain injuries, CT scanning uses a computer program that performs a numerical integral calculation (the inverse Radon transform) on the measured x-ray series to estimate how much of an x-ray beam is absorbed in a small volume of the brain. Typically the information is presented as cross sections of the brain.^[2]

In approximation, the denser a material is, the whiter a volume of it will appear on the scan (just as in the more familiar "flat" X-rays). CT scans are primarily used for evaluating swelling from tissue damage in the brain and in assessment of ventricle size. Modern CT scanning can provide reasonably good images in a matter of minutes.

Diffuse optical imaging

Diffuse optical imaging (DOI) or diffuse optical tomography (DOT) is a medical imaging modality which uses near infrared light to generate images of the body. The technique measures the optical absorption of haemoglobin, and relies on the absorption spectrum of haemoglobin varying with its oxygenation status.

Event-related optical signal

Event-related optical signal (EROS) is a brain-scanning technique which uses infrared light through optical fibers to measure changes in optical properties of active areas of the cerebral cortex. Whereas techniques such as diffuse optical imaging (DOT) and near infrared spectroscopy (NIRS) measure optical absorption of haemoglobin, and thus are based on blood flow, EROS takes advantage of the scattering properties of the neurons themselves, and thus provides a much more direct measure of cellular activity. EROS can pinpoint activity in the brain within millimeters (spatially) and within milliseconds (temporally). Its biggest downside is the inability to detect activity more than a few centimeters deep. EROS is a new, relatively inexpensive technique that is non-invasive to the test subject. It was developed at the University of Illinois at Urbana-Champaign where it is now used in the Cognitive Neuroimaging Laboratory of Dr. Gabriele Gratton and Dr. Monica Fabiani.

Magnetic resonance imaging

Magnetic resonance imaging (MRI) uses magnetic fields and radio waves to produce high quality two- or three-dimensional images of brain structures without use of ionizing radiation (X-rays) or radioactive tracers. During an MRI, a large cylindrical magnet creates a magnetic field around the head of the patient through which radio waves are sent. When the magnetic field is imposed, each point in space has a unique radio frequency at which the signal is received and transmitted (Preuss). Sensors read the frequencies and a computer uses the information to construct an image. The detection mechanisms are so precise that changes in structures over time can be detected.^[1]

Using MRI, scientists can create images of both surface and subsurface structures with a high degree of anatomical detail. MRI scans can produce cross sectional images in any direction from top to bottom, side to side, or front to back. The problem with original MRI technology was that while it provides a detailed assessment of the physical appearance, water content, and many kinds of subtle derangements of structure of the brain (such as inflammation or bleeding), it fails to provide information about the metabolism of the brain (i.e. how actively it is functioning) at the time of imaging. A distinction is therefore made between "MRI imaging" and "functional MRI imaging" (fMRI), where MRI provides only structural information on the brain while fMRI yields both structural and functional data.



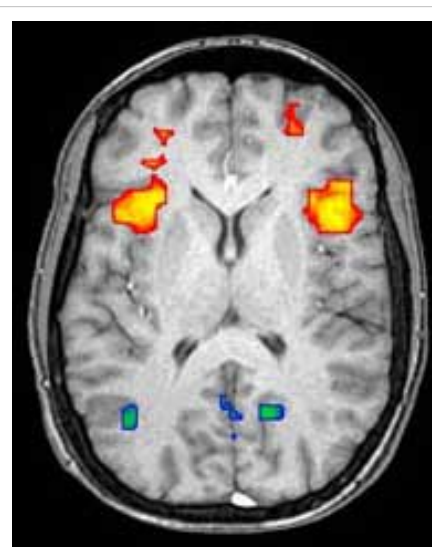
Sagittal MRI slice at the midline.

Functional magnetic resonance imaging

Functional magnetic resonance imaging (fMRI) relies on the paramagnetic properties of oxygenated and deoxygenated hemoglobin to see images of changing blood flow in the brain associated with neural activity. This allows images to be generated that reflect which brain structures are activated (and how) during performance of different tasks.

Most fMRI scanners allow subjects to be presented with different visual images, sounds and touch stimuli, and to make different actions such as pressing a button or moving a joystick. Consequently, fMRI can be used to reveal brain structures and processes associated with perception, thought and action. The resolution of fMRI is about 2-3 millimeters at present, limited by the spatial spread of the hemodynamic response to neural activity. It has largely superseded PET for the study of brain activation patterns. PET, however, retains the significant advantage of being able to identify specific brain receptors (or transporters) associated with particular neurotransmitters through its ability to image radiolabelled receptor "ligands" (receptor ligands are any chemicals that stick to receptors).

As well as research on healthy subjects, fMRI is increasingly used for the medical diagnosis of disease. Because fMRI is exquisitely sensitive to blood flow, it is extremely sensitive to early changes in the brain resulting from ischemia (abnormally low blood flow), such as the changes which follow stroke. Early diagnosis of certain types of



Axial MRI slice at the level of the basal ganglia, showing fMRI BOLD signal changes overlaid in red (increase) and blue (decrease) tones.

stroke is increasingly important in neurology, since substances which dissolve blood clots may be used in the first few hours after certain types of stroke occur, but are dangerous to use afterwards. Brain changes seen on fMRI may help to make the decision to treat with these agents. With between 72% and 90% accuracy where chance would achieve 0.8%,^[3] fMRI techniques can decide which of a set of known images the subject is viewing.^[4]

Electroencephalography

Electroencephalography (EEG) is an imaging technique used to measure the electric fields in the brain via electrodes placed on the scalp of a human. EEG offers a very direct measurement of neural electrical activity with very high temporal resolution but relatively low spatial resolution.^[5]

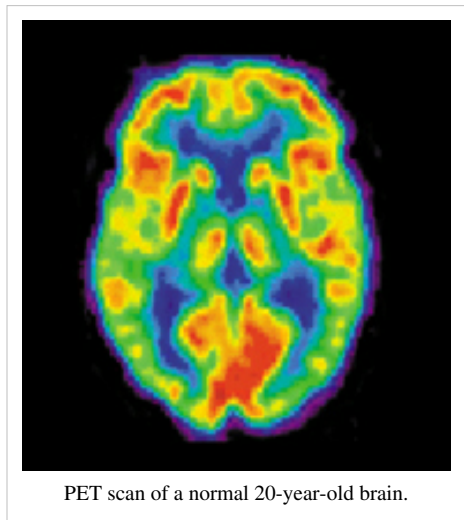
Magnetoencephalography

Magnetoencephalography (MEG) is an imaging technique used to measure the magnetic fields produced by electrical activity in the brain via extremely sensitive devices such as superconducting quantum interference devices (SQUIDs). MEG offers a very direct measurement neural electrical activity (compared to fMRI for example) with very high temporal resolution but relatively low spatial resolution. The advantage of measuring the magnetic fields produced by neural activity is that they are not distorted by surrounding tissue, unlike the electric fields measured by EEG (particularly the skull and scalp).

There are many uses for the MEG, including assisting surgeons in localizing a pathology, assisting researchers in determining the function of various parts of the brain, neurofeedback, and others.

Positron emission tomography

Positron emission tomography (PET) measures emissions from radioactively labeled metabolically active chemicals that have been injected into the bloodstream. The emission data are computer-processed to produce 2- or 3-dimensional images of the distribution of the chemicals throughout the brain.^[6] The positron emitting radioisotopes used are produced by a cyclotron, and chemicals are labeled with these radioactive atoms. The labeled compound, called a *radiotracer*, is injected into the bloodstream and eventually makes its way to the brain. Sensors in the PET scanner detect the radioactivity as the compound accumulates in various regions of the brain. A computer uses the data gathered by the sensors to create multicolored 2- or 3-dimensional images that show where the compound acts in the brain. Especially useful are a wide array of ligands used to map different aspects of neurotransmitter activity, with by far the most commonly used PET tracer being a labeled form of glucose (see FDG).



The greatest benefit of PET scanning is that different compounds can show blood flow and oxygen and glucose metabolism in the tissues of the working brain. These measurements reflect the amount of brain activity in the various regions of the brain and allow to learn more about how the brain works. PET scans were superior to all other metabolic imaging methods in terms of resolution and speed of completion (as little as 30 seconds), when they first became available. The improved resolution permitted better study to be made as to the area of the brain activated by a particular task. The biggest drawback of PET scanning is that because the radioactivity decays rapidly, it is limited to monitoring short tasks.^[7] Before fMRI technology came online, PET scanning was the preferred method of functional (as opposed to structural) brain imaging, and it still continues to make large contributions to neuroscience.

PET scanning is also used for diagnosis of brain disease, most notably because brain tumors, strokes, and neuron-damaging diseases which cause dementia (such as Alzheimer's disease) all cause great changes in brain metabolism, which in turn causes easily detectable changes in PET scans. PET is probably most useful in early cases of certain dementias (with classic examples being Alzheimer's disease and Pick's disease) where the early damage is too diffuse and makes too little difference in brain volume and gross structure to change CT and standard MRI images enough to be able to reliably differentiate it from the "normal" range of cortical atrophy which occurs with aging (in many but not all) persons, and which does *not* cause clinical dementia.

Single photon emission computed tomography

Single photon emission computed tomography (SPECT) is similar to PET and uses gamma ray emitting radioisotopes and a gamma camera to record data that a computer uses to construct two- or three-dimensional images of active brain regions^[8] SPECT relies on an injection of radioactive tracer, which is rapidly taken up by the brain but does not redistribute. Uptake of SPECT agent is nearly 100% complete within 30 – 60s, reflecting cerebral blood flow (CBF) at the time of injection. These properties of SPECT make it particularly well suited for epilepsy imaging, which is usually made difficult by problems with patient movement and variable seizure types. SPECT provides a "snapshot" of cerebral blood flow since scans can be acquired after seizure termination (so long as the radioactive tracer was injected at the time of the seizure). A significant limitation of SPECT is its poor resolution (about 1 cm) compared to that of MRI.

Like PET, SPECT also can be used to differentiate different kinds of disease processes which produce dementia, and it is increasingly used for this purpose. Neuro-PET has a disadvantage of requiring use of tracers with half-lives of at most 110 minutes, such as FDG. These must be made in a cyclotron, and are expensive or even unavailable if necessary transport times are prolonged more than a few half-lives. SPECT, however, is able to make use of tracers with much longer half-lives, such as technetium-99m, and as a result, is far more widely available.

See also

- Brain mapping
 - Functional neuroimaging
 - functional near-infrared imaging
 - History of brain imaging
 - Human Genome Project
 - Magnetic resonance imaging
 - Magnetoencephalography
 - Medical imaging
 - Neuroimaging software
 - Statistical parametric mapping
 - Transcranial magnetic stimulation
 - Voxel-based morphometry
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External links

- The Whole Brain Atlas @ Harvard ^[9]
- The McConnell Brain Imaging Center, McGill University ^[10]
- The American Society of Neuroimaging (ASN) ^[11].
- UCLA Neuroimaging Training Program ^[12].
- Laboratory of Neuro Imaging ^[13] at UCLA
- A Neuroimaging portal ^[14]
- BrainMapping.org, *a free BrainMapping community information portal* ^[15]
- Lecture notes on mathematical aspects of neuroimaging ^[16] by Will Penny, University College London
- "Transcranial Magnetic Stimulation" ^[17] by Michael Leventon in association with MIT AI Lab.
- *Foundations of fMRI* ^[18] by Jamie Shorey.
- International Society for Neuroimaging in Psychiatry (ISNIP) ^[19]

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- [6] Nilsson, page 57
- [7] Nilson, pg. 60
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- [16] <http://www.fil.ion.ucl.ac.uk/~wpenny/mbi/>
[17] <http://www.ai.mit.edu/projects/medical-vision/surgery/tms.html>
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[19] <http://www.isnip.org/>

Chemical imaging

Chemical imaging is the analytical capability (as quantitative - mapping) to create a visual image from simultaneous measurement of spectra (as quantitative - chemical) and spatial, time informations.^{[1] [2]} The technique is most often applied to either solid or gel samples, and has applications in chemistry, biology^{[3] [4] [5] [6] [7] [8]}, medicine^{[9] [10]}, pharmacy^[11] (see also for example: Chemical Imaging Without Dyeing^[12]), food science, biotechnology^{[13] [14]}, agriculture and industry (see for example: NIR Chemical Imaging in Pharmaceutical Industry^[15] and Pharmaceutical Process Analytical Technology: ^[16]). NIR, IR and Raman chemical imaging is also referred to as hyperspectral, spectroscopic, spectral or multispectral imaging (also see microspectroscopy). However, other ultra-sensitive and selective, chemical imaging techniques are also in use that involve either UV-visible or fluorescence microspectroscopy. Chemical imaging techniques can be used to analyze samples of all sizes, from the single molecule^{[17] [18]} to the cellular level in biology and medicine^{[19] [20] [21]}, and to images of planetary systems in astronomy, but different instrumentation is employed for making observations on such widely different systems.

Chemical imaging instrumentation is composed of three components: a radiation source to illuminate the sample, a spectrally selective element, and usually a detector array (the camera) to collect the images. When many stacked spectral channels (wavelengths) are collected for different locations of the microspectrometer focus on a line or planar array in the focal plane, the data is called hyperspectral; fewer wavelength data sets are called multispectral. The data format is called a hypercube. The data set may be visualized as a three-dimensional block of data spanning two spatial dimensions (x and y), with a series of wavelengths (λ) making up the third (spectral) axis. The hypercube can be visually and mathematically treated as a series of spectrally resolved images (each image plane corresponding to the image at one wavelength) or a series of spatially resolved spectra. The analyst may choose to view the spectrum measured at a particular spatial location; this is useful for chemical identification. Alternatively, selecting an image plane at a particular wavelength can highlight the spatial distribution of sample components, provided that their spectral signatures are different at the selected wavelength.

Many materials, both manufactured and naturally occurring, derive their functionality from the spatial distribution of sample components. For example, extended release pharmaceutical formulations can be achieved by using a coating that acts as a barrier layer. The release of active ingredient is controlled by the presence of this barrier, and imperfections in the coating, such as discontinuities, may result in altered performance. In the semi-conductor industry, irregularities or contaminants in silicon wafers or printed micro-circuits can lead to failure of these components. The functionality of biological systems is also dependent upon chemical gradients – a single cell, tissue, and even whole organs function because of the very specific arrangement of components. It has been shown that even small changes in chemical composition and distribution may be an early indicator of disease.

Any material that depends on chemical gradients for functionality may be amenable to study by an analytical technique that couples spatial and chemical characterization. To efficiently and effectively design and manufacture such materials, the 'what' and the 'where' must both be measured. The demand for this type of analysis is increasing as manufactured materials become more complex. Chemical imaging techniques not only permit visualization of the spatially resolved chemical information that is critical to understanding modern manufactured products, but it is also a non-destructive technique so that samples are preserved for further testing.

History

Commercially available laboratory-based chemical imaging systems emerged in the early 1990s (ref. 1-5). In addition to economic factors, such as the need for sophisticated electronics and extremely high-end computers, a significant barrier to commercialization of infrared imaging was that the focal plane array (FPA) needed to read IR images were not readily available as commercial items. As high-speed electronics and sophisticated computers became more commonplace, and infrared cameras became readily commercially available, laboratory chemical imaging systems were introduced.

Initially used for novel research in specialized laboratories, chemical imaging became a more commonplace analytical technique used for general R&D, quality assurance (QA) and quality control (QC) in less than a decade. The rapid acceptance of the technology in a variety of industries (pharmaceutical, polymers, semiconductors, security, forensics and agriculture) rests in the wealth of information characterizing both chemical composition and morphology. The parallel nature of chemical imaging data makes it possible to analyze multiple samples simultaneously for applications that require high throughput analysis in addition to characterizing a single sample.

Principles

Chemical imaging shares the fundamentals of vibrational spectroscopic techniques, but provides additional information by way of the simultaneous acquisition of spatially resolved spectra. It combines the advantages of digital imaging with the attributes of spectroscopic measurements. Briefly, vibrational spectroscopy measures the interaction of light with matter. Photons that interact with a sample are either absorbed or scattered; photons of specific energy are absorbed, and the pattern of absorption provides information, or a fingerprint, on the molecules that are present in the sample.

On the other hand, in terms of the observation setup, chemical imaging can be carried out in one of the following modes: (optical) absorption, emission (fluorescence), (optical) transmission or scattering (Raman). A consensus currently exists that the fluorescence (emission) and Raman scattering modes are the most sensitive and powerful, but also the most expensive.

In a transmission measurement, the radiation goes through a sample and is measured by a detector placed on the far side of the sample. The energy transferred from the incoming radiation to the molecule(s) can be calculated as the difference between the quantity of photons that were emitted by the source and the quantity that is measured by the detector. In a diffuse reflectance measurement, the same energy difference measurement is made, but the source and detector are located on the same side of the sample, and the photons that are measured have re-emerged from the illuminated side of the sample rather than passed through it. The energy may be measured at one or multiple wavelengths; when a series of measurements are made, the response curve is called a spectrum.

A key element in acquiring spectra is that the radiation must somehow be energy selected – either before or after interacting with the sample. Wavelength selection can be accomplished with a fixed filter, tunable filter, spectrograph, an interferometer, or other devices. For a fixed filter approach, it is not efficient to collect a significant number of wavelengths, and multispectral data are usually collected. Interferometer-based chemical imaging requires that entire spectral ranges be collected, and therefore results in hyperspectral data. Tunable filters have the flexibility to provide either multi- or hyperspectral data, depending on analytical requirements.

Spectra may be measured one point at a time using a single element detector (single-point mapping), as a line-image using a linear array detector (typically 16 to 28 pixels) (linear array mapping), or as a two-dimensional image using a Focal Plane Array (FPA)(typically 256 to 16,384 pixels) (FPA imaging). For single-point the sample is moved in the x and y directions point-by-point using a computer-controlled stage. With linear array mapping, the sample is moved line-by-line with a computer-controlled stage. FPA imaging data are collected with a two-dimensional FPA detector, hence capturing the full desired field-of-view at one time for each individual wavelength, without having to move the sample. FPA imaging, with its ability to collect tens of thousands of spectra simultaneously is orders of

magnitude faster than linear arrays which can typically collect 16 to 28 spectra simultaneously, which are in turn much faster than single-point mapping.

Terminology

Some words common in spectroscopy, optical microscopy and photography have been adapted or their scope modified for their use in chemical imaging. They include: resolution, field of view and magnification. There are two types of resolution in chemical imaging. The spectral resolution refers to the ability to resolve small energy differences; it applies to the spectral axis. The spatial resolution is the minimum distance between two objects that is required for them to be detected as distinct objects. The spatial resolution is influenced by the field of view, a physical measure of the size of the area probed by the analysis. In imaging, the field of view is a product of the magnification and the number of pixels in the detector array. The magnification is a ratio of the physical area of the detector array divided by the area of the sample field of view. Higher magnifications for the same detector image a smaller area of the sample.

Types of vibrational chemical imaging instruments

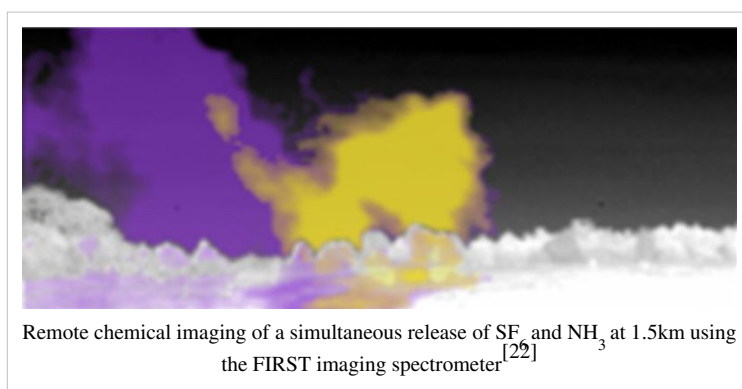
Chemical imaging has been implemented for mid-infrared, near-infrared spectroscopy and Raman spectroscopy. As with their bulk spectroscopy counterparts, each imaging technique has particular strengths and weaknesses, and are best suited to fulfill different needs.

Mid-infrared chemical imaging

Mid-infrared (MIR) spectroscopy probes fundamental molecular vibrations, which arise in the spectral range 2,500-25,000 nm. Commercial imaging implementations in the MIR region typically employ Fourier Transform Infrared (FT-IR) interferometers and the range is more commonly presented in wavenumber, 4,000 – 400 cm^{-1} . The MIR absorption bands tend to be relatively narrow and well-resolved; direct spectral interpretation is often possible by an experienced spectroscopist. MIR spectroscopy can distinguish subtle changes in chemistry and structure, and is often used for the identification of unknown materials. The absorptions in this spectral range are relatively strong; for this reason, sample presentation is important to limit the amount of material interacting with the incoming radiation in the MIR region. Most data collected in this range is collected in transmission mode through thin sections (~10 micrometres) of material. Water is a very strong absorber of MIR radiation and wet samples often require advanced sampling procedures (such as attenuated total reflectance). Commercial instruments include point and line mapping, and imaging. All employ an FT-IR interferometer as wavelength selective element and light source.

For types of MIR microscope, see [Microscopy#Infrared microscopy](#).

Atmospheric windows in the infrared spectrum are also employed to perform chemical imaging remotely. In these spectral regions the atmospheric gases (mainly water and CO_2) present low absorption and allow infrared viewing over kilometer distances. Target molecules can then be viewed using the selective absorption/emission processes described above. An example of the chemical imaging of a simultaneous release of SF_6 and NH_3 is shown in the image.



Near-infrared chemical imaging

The analytical near infrared (NIR) region spans the range from approximately 700-2,500 nm. The absorption bands seen in this spectral range arise from overtones and combination bands of O-H, N-H, C-H and S-H stretching and bending vibrations. Absorption is one to two orders of magnitude smaller in the NIR compared to the MIR; this phenomenon eliminates the need for extensive sample preparation. Thick and thin samples can be analyzed without any sample preparation, it is possible to acquire NIR chemical images through some packaging materials, and the technique can be used to examine hydrated samples, within limits. Intact samples can be imaged in transmittance or diffuse reflectance.

The lineshapes for overtone and combination bands tend to be much broader and more overlapped than for the fundamental bands seen in the MIR. Often, multivariate methods are used to separate spectral signatures of sample components. NIR chemical imaging is particularly useful for performing rapid, reproducible and non-destructive analyses of known materials^{[23] [24]}. NIR imaging instruments are typically based on one of two platforms: imaging using a tunable filter and broad band illumination, and line mapping employing an FT-IR interferometer as the wavelength filter and light source.

Raman chemical imaging

The Raman shift chemical imaging spectral range spans from approximately 50 to 4,000 cm^{-1} ; the actual spectral range over which a particular Raman measurement is made is a function of the laser excitation frequency. The basic principle behind Raman spectroscopy differs from the MIR and NIR in that the x-axis of the Raman spectrum is measured as a function of energy shift (in cm^{-1}) relative to the frequency of the laser used as the source of radiation. Briefly, the Raman spectrum arises from inelastic scattering of incident photons, which requires a change in polarizability with vibration, as opposed to infrared absorption, which requires a change in dipole moment with vibration. The end result is spectral information that is similar and in many cases complementary to the MIR. The Raman effect is weak - only about one in 10^7 photons incident to the sample undergoes Raman scattering. Both organic and inorganic materials possess a Raman spectrum; they generally produce sharp bands that are chemically specific. Fluorescence is a competing phenomenon and, depending on the sample, can overwhelm the Raman signal, for both bulk spectroscopy and imaging implementations.

Raman chemical imaging requires little or no sample preparation. However, physical sample sectioning may be used to expose the surface of interest, with care taken to obtain a surface that is as flat as possible. The conditions required for a particular measurement dictate the level of invasiveness of the technique, and samples that are sensitive to high power laser radiation may be damaged during analysis. It is relatively insensitive to the presence of water in the sample and is therefore useful for imaging samples that contain water such as biological material.

Fluorescence imaging (visible and NIR)

This emission microspectroscopy mode is the most sensitive in both visible and FT-NIR microspectroscopy, and has therefore numerous biomedical, biotechnological and agricultural applications. There are several powerful, highly specific and sensitive fluorescence techniques that are currently in use, or still being developed; among the former are FLIM, FRAP, FRET and FLIM-FRET; among the latter are NIR fluorescence and probe-sensitivity enhanced NIR fluorescence microspectroscopy and nanospectroscopy techniques (see "Further reading" section).

Sampling and samples

The value of imaging lies in the ability to resolve spatial heterogeneities in solid-state or gel/gel-like samples. Imaging a liquid or even a suspension has limited use as constant sample motion serves to average spatial information, unless ultra-fast recording techniques are employed as in fluorescence correlation microspectroscopy or FLIM observations where a single molecule may be monitored at extremely high (photon) detection speed. High-throughput experiments (such as imaging multi-well plates) of liquid samples can however provide valuable

information. In this case, the parallel acquisition of thousands of spectra can be used to compare differences between samples, rather than the more common implementation of exploring spatial heterogeneity within a single sample.

Similarly, there is no benefit in imaging a truly homogeneous sample, as a single point spectrometer will generate the same spectral information. Of course the definition of homogeneity is dependent on the spatial resolution of the imaging system employed. For MIR imaging, where wavelengths span from 3-10 micrometres, objects on the order of 5 micrometres may theoretically be resolved. The sampled areas are limited by current experimental implementations because illumination is provided by the interferometer. Raman imaging may be able to resolve particles less than 1 micrometre in size, but the sample area that can be illuminated is severely limited. With Raman imaging, it is considered impractical to image large areas and, consequently, large samples. FT-NIR chemical/hyperspectral imaging usually resolves only larger objects (>10 micrometres), and is better suited for large samples because illumination sources are readily available. However, FT-NIR microspectroscopy was recently reported to be capable of about 1.2 micron (micrometer) resolution in biological samples^[25] Furthermore, two-photon excitation FCS experiments were reported to have attained 15 nanometer resolution on biomembrane thin films with a special coincidence photon-counting setup.

Detection limit

The concept of the detection limit for chemical imaging is quite different than for bulk spectroscopy, as it depends on the sample itself. Because a bulk spectrum represents an average of the materials present, the spectral signatures of trace components are simply overwhelmed by dilution. In imaging however, each pixel has a corresponding spectrum. If the physical size of the trace contaminant is on the order of the pixel size imaged on the sample, its spectral signature will likely be detectable. If however, the trace component is dispersed homogeneously (relative to pixel image size) throughout a sample, it will not be detectable. Therefore, detection limits of chemical imaging techniques are strongly influenced by particle size, the chemical and spatial heterogeneity of the sample, and the spatial resolution of the image.

Data analysis

Data analysis methods for chemical imaging data sets typically employ mathematical algorithms common to single point spectroscopy or to image analysis. The reasoning is that the spectrum acquired by each detector is equivalent to a single point spectrum; therefore pre-processing, chemometrics and pattern recognition techniques are utilized with the similar goal to separate chemical and physical effects and perform a qualitative or quantitative characterization of individual sample components. In the spatial dimension, each chemical image is equivalent to a digital image and standard image analysis and robust statistical analysis can be used for feature extraction.

See also

- Multispectral image
- Microspectroscopy
- Imaging spectroscopy

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External links

- NIR Chemical Imaging in Pharmaceutical Industry^[15]
- Pharmaceutical Process Analytical Technology:^[16]
- NIR Chemical Imaging for Counterfeit Pharmaceutical Product Analysis^[27]
- Chemical Imaging: Potential New Crime Busting Tool^[28]
- Applications of Chemical Imaging in Research^[29]

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[27] <http://www.spectroscopymag.com/spectroscopy/Near-IR+Spectroscopy/NIR-Chemical-Imaging-for-Counterfeit-Pharmaceutical/ArticleStandard/Article/detail/406629>

[28] <http://www.sciencedaily.com/releases/2007/08/070802103435.htm>

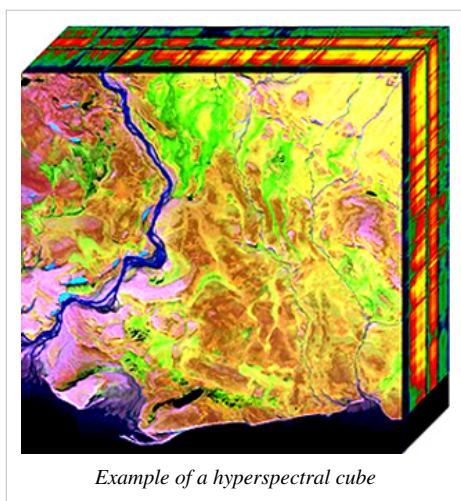
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Hyperspectral imaging

Hyperspectral imaging collects and processes information from across the electromagnetic spectrum. Unlike the human eye, which just sees visible light, hyperspectral imaging is more like the eyes of the mantis shrimp, which can see visible light as well as from the ultraviolet to infrared. Hyperspectral capabilities enable the mantis shrimp to recognize different types of coral, prey, or predators, all which may appear as the same color to the human eye.

Humans build sensors and processing systems to provide the same type of capability for application in agriculture, mineralogy, physics, and surveillance. Hyperspectral sensors look at objects using a vast portion of the electromagnetic spectrum. Certain objects leave unique 'fingerprints' across the electromagnetic spectrum. These 'fingerprints' are known as spectral signatures and enable identification of the materials that make up a scanned object. For example, having the spectral signature for oil helps mineralogists find new oil fields.

Acquisition and Analysis



Example of a hyperspectral cube

Hyperspectral sensors collect information as a set of 'images'. Each image represents a range of the electromagnetic spectrum and is also known as a spectral band. These 'images' are then combined and form a three dimensional hyperspectral cube for processing and analysis.

Hyperspectral cubes are generated from airborne sensors like the NASA's *Airborne Visible/Infrared Imaging Spectrometer* (AVIRIS), or from satellites like NASA's Hyperion.^[1] However, for many development and validation studies handheld sensors are used.^[2]

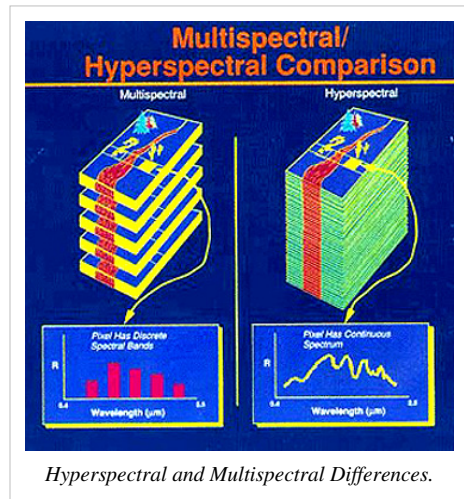
The precision of these sensors is typically measured in spectral resolution, which is the width of each band of the spectrum that is captured. If the scanner picks up on a large number of fairly narrow frequency bands, it is possible to identify objects even if said objects are only captured in a handful of pixels. However, spatial resolution is

a factor in addition to spectral resolution. If the pixels are too large, then multiple objects are captured in the same pixel and become difficult to identify. If the pixels are too small, then the energy captured by each sensor-cell is low, and the decreased signal-to-noise ratio reduces the reliability of measured features.

MicroMSI, Opticks and Envi are three remote sensing applications that support the processing and analysis of hyperspectral data. The acquisition and processing of hyperspectral images is also referred to as imaging spectroscopy.

Differences between hyperspectral and multispectral imaging

Hyperspectral imaging is part of a class of techniques commonly referred to as spectral imaging or spectral analysis. Hyperspectral imaging is related to multispectral imaging. The distinction between hyperspectral and multispectral is usually defined as the number of spectral bands. Multispectral data contains from several to tens of bands. Hyperspectral data contains dozens to hundreds of bands. However, hyperspectral imaging may be best defined by the manner in which the data is collected. Hyperspectral data is a set of contiguous bands (usually by one sensor). Multispectral is a set of optimally chosen spectral bands that are typically not contiguous and can be collected from multiple sensors.



Applications

Hyperspectral remote sensing is used in a wide array of real-life applications. Although originally developed for mining and geology (the ability of hyperspectral imaging to identify various minerals makes it ideal for the mining and oil industries, where it can be used to look for ore and oil^{[2] [3]}) it has now spread into fields as widespread as ecology and surveillance, as well as historical manuscript research such as the imaging of the Archimedes Palimpsest. This technology is continually becoming more available to the public, and has been used in a wide variety of ways. Organizations such as NASA and the USGS have catalogues of various minerals and their spectral signatures, and have posted them online to make them readily available for researchers.

Agriculture

Although the costs of acquiring hyperspectral images is typically high, for specific crops and in specific climates hyperspectral remote sensing is used more and more for monitoring the development and health of crops. In Australia work is underway to use imaging spectrometers to detect grape variety, and develop an early warning system for disease outbreaks.^[4] Furthermore work is underway to use hyperspectral data to detect the chemical composition of plants^[5] which can be used to detect the nutrient and water status of wheat in irrigated systems^[6]

Mineralogy

The original field of development for hyperspectral remote sensing, hyperspectral sensing of minerals is now well developed. Many minerals can be identified from images, and their relation to the presence of valuable minerals such as gold and diamonds is well understood. Currently the move is towards understanding the relation between oil and gas leakages from pipelines and natural wells; their effect on the vegetation and the spectral signatures. Recent work includes the PhD dissertations of Werff^[7] and Noomen^[8].

Physics

Physicists use an electron microscopy technique that involves microanalysis using either Energy dispersive X-ray spectroscopy (EDS), Electron energy loss spectroscopy (EELS), Infrared Spectroscopy (IR), Raman Spectroscopy, or cathodoluminescence (CL) spectroscopy, in which the entire spectrum measured at each point is recorded. EELS hyperspectral imaging is performed in a scanning transmission electron microscope (STEM); EDS and CL mapping can be performed in STEM as well, or in a scanning electron microscope or electron probe microanalyzer (EPMA).

Often, multiple techniques (EDS, EELS, CL) are used simultaneously.

In a "normal" mapping experiment, an image of the sample will be made that is simply the intensity of a particular emission mapped in an XY raster. For example, an EDS map could be made of a steel sample, in which iron x-ray intensity is used for the intensity grayscale of the image. Dark areas in the image would indicate not-iron-bearing impurities. This could potentially give misleading results; if the steel contained tungsten inclusions, for example, the high atomic number of tungsten could result in bremsstrahlung radiation that made the iron-free areas *appear* to be rich in iron.

By hyperspectral mapping, instead, the entire spectrum at each mapping point is acquired, and a quantitative analysis can be performed by computer post-processing of the data, and a quantitative map of iron content produced. This would show which areas contained no iron, despite the anomalous x-ray counts caused by bremsstrahlung. Because EELS core-loss edges are small signals on top of a large background, hyperspectral imaging allows large improvements to the quality of EELS chemical maps.

Similarly, in CL mapping, small shifts in the peak emission energy could be mapped, which would give information regarding slight chemical composition changes or changes in the stress state of a sample.

Surveillance

Hyperspectral surveillance is the implementation of hyperspectral scanning technology for surveillance purposes. Hyperspectral imaging is particularly useful in military surveillance because of measures that military entities now take to avoid airborne surveillance. Airborne surveillance has been in effect since soldiers used tethered balloons to spy on troops during the American Civil War, and since that time we have learned not only to hide from the naked eye, but to mask our heat signature to blend in to the surroundings and avoid infrared scanning, as well. The idea that drives hyperspectral surveillance is that hyperspectral scanning draws information from such a large portion of the light spectrum that any given object should have unique spectral signature in at least a few of the many bands that get scanned.^[1]

Advantages and disadvantages

The primary advantages to hyperspectral imaging is that, because an entire spectrum is acquired at each point, the operator needs no prior knowledge of the sample, and post-processing allows all available information from the dataset to be mined.

The primary disadvantages are cost and complexity. Fast computers, sensitive detectors, and large data storage capacities are needed for analyzing hyperspectral data. Significant data storage capacity is necessary since hyperspectral cubes are large multi-dimensional datasets, potentially exceeding hundreds of megabytes. All of these factors greatly increase the cost of acquiring and processing hyperspectral data. Also, one of the hurdles that researchers have had to face is finding ways to program hyperspectral satellites to sort through data on their own and transmit only the most important images, as both transmission and storage of that much data could prove difficult and costly.^[1] As a relatively new analytical technique, the full potential of hyperspectral imaging has not yet been realized.

See also

- Airborne Real-time Cueing Hyperspectral Enhanced Reconnaissance
- Full Spectral Imaging
- Multi-spectral image
- Chemical imaging
- Remote Sensing
- Sensor fusion
- ERDAS IMAGINE

External links

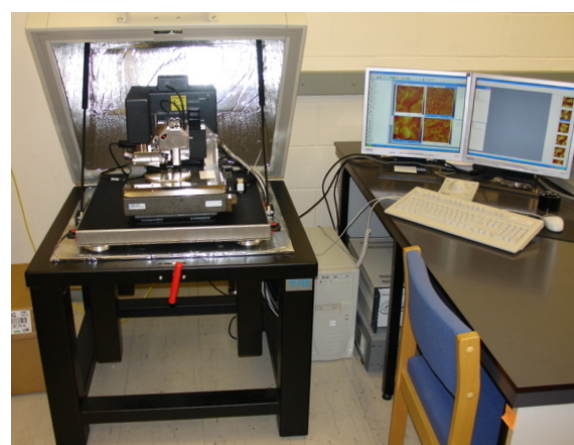
- Opticks^[9] - open source, remote sensing application and development framework.
- ITT Visual Information Solutions - ENVI Hyperspectral Image Processing Software^[10]
- A Hyperspectral Imaging Prototype^[11] Fourier transform spectroscopy is combined with Fabry-Perot interferometry
- Middleton Research^[12] Hyperspectral Imaging products, custom engineering solutions
- Photon etc.^[13] Hyperspectral Imaging Systems
- UmBio - Evince. Hyperspectral image analysis in real-time. Visual information solutions, see industrial demo movies^[14]
- A Matlab Hyperspectral Toolbox^[15]
- Telops Hyper-Cam^[16] Commercial infrared hyperspectral camera

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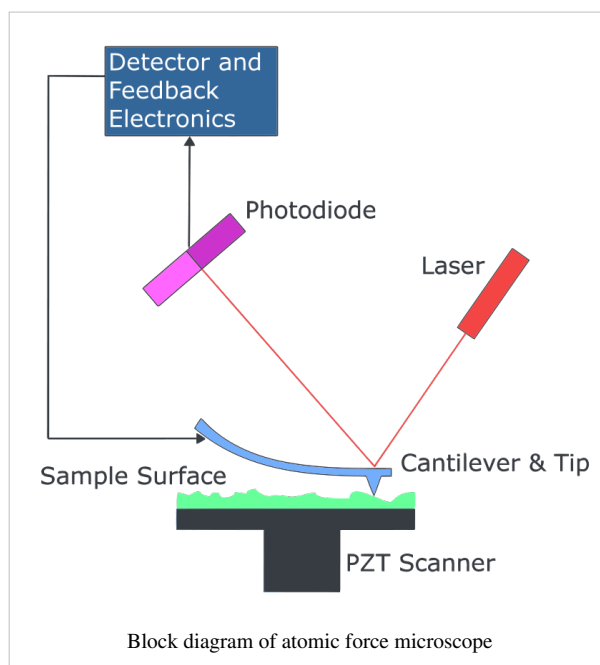
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- [9] <http://opticks.org/>
- [10] <http://www.ittvis.com/ProductServices/ENVI.aspx>
- [11] http://www.inrim.it/res/hyperspectral_imaging/
- [12] <http://www.middletonresearch.com>
- [13] <http://photonetc.com/index.php?lan=en&sec=300&sub1=3000&sub2=1023>
- [14] <http://beta.umbio.com/Public%20files/Products/Evince%20Image/EvinceImage.aspx>
- [15] <http://matlabhyperspec.sourceforge.net/>
- [16] <http://www.hyper-cam.com/>

Atomic force microscope

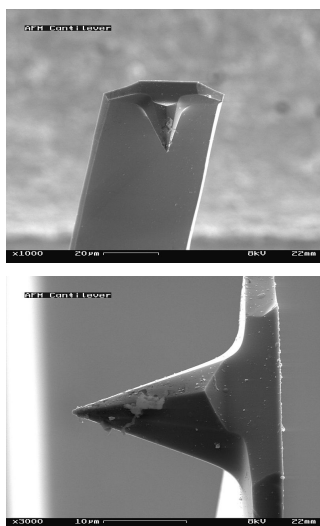
Atomic force microscopy (AFM) or scanning force microscopy (SFM) is a very high-resolution type of scanning probe microscopy, with demonstrated resolution of fractions of a nanometer, more than 1000 times better than the optical diffraction limit. The precursor to the AFM, the scanning tunneling microscope, was developed by Gerd Binnig and Heinrich Rohrer in the early 1980s at IBM Research - Zurich, a development that earned them the Nobel Prize for Physics in 1986. Binnig, Quate and Gerber invented the first atomic force microscope (also abbreviated as AFM) in 1986. The AFM is one of the foremost tools for imaging, measuring, and manipulating matter at the nanoscale. The information is gathered by "feeling" the surface with a mechanical probe. Piezoelectric elements that facilitate tiny but accurate and precise movements on (electronic) command enable the very precise scanning. In some variations, electric potentials can also be scanned using conducting cantilevers. In newer more advanced versions, currents can even be passed through the tip to probe the electrical conductivity or transport of the underlying surface, but this is much more challenging with very few groups reporting reliable data.



A commercial AFM setup



Basic principles



Electron micrograph of a used AFM cantilever image width ~100 micrometers (top) and ~30 micrometers (bottom)

The AFM consists of a cantilever with a sharp tip (probe) at its end that is used to scan the specimen surface. The cantilever is typically silicon or silicon nitride with a tip radius of curvature on the order of nanometers. When the tip is brought into proximity of a sample surface, forces between the tip and the sample lead to a deflection of the cantilever according to Hooke's law. Depending on the situation, forces that are measured in AFM include

mechanical contact force, van der Waals forces, capillary forces, chemical bonding, electrostatic forces, magnetic forces (see magnetic force microscope, MFM), Casimir forces, solvation forces, etc. As well as force, additional quantities may simultaneously be measured through the use of specialized types of probe (see scanning thermal microscopy, photothermal microspectroscopy, etc.). Typically, the deflection is measured using a laser spot reflected from the top surface of the cantilever into an array of photodiodes. Other methods that are used include optical interferometry, capacitive sensing or piezoresistive AFM cantilevers. These cantilevers are fabricated with piezoresistive elements that act as a strain gauge. Using a Wheatstone bridge, strain in the AFM cantilever due to deflection can be measured, but this method is not as sensitive as laser deflection or interferometry.

If the tip was scanned at a constant height, a risk would exist that the tip collides with the surface, causing damage. Hence, in most cases a feedback mechanism is employed to adjust the tip-to-sample distance to maintain a constant force between the tip and the sample. Traditionally, the sample is mounted on a piezoelectric tube, that can move the sample in the z direction for maintaining a constant force, and the x and y directions for scanning the sample. Alternatively a 'tripod' configuration of three piezo crystals may be employed, with each responsible for scanning in the x, y and z directions. This eliminates some of the distortion effects seen with a tube scanner. In newer designs, the tip is mounted on a vertical piezo scanner while the sample is being scanned in X and Y using another piezo block. The resulting map of the area $s = f(x, y)$ represents the topography of the sample.

The AFM can be operated in a number of modes, depending on the application. In general, possible imaging modes are divided into static (also called *contact*) modes and a variety of dynamic (or non-contact) modes where the cantilever is vibrated.

Imaging modes

The primary modes of operation are static (contact) mode and dynamic mode. In the static mode operation, the static tip deflection is used as a feedback signal. Because the measurement of a static signal is prone to noise and drift, low stiffness cantilevers are used to boost the deflection signal. However, close to the surface of the sample, attractive forces can be quite strong, causing the tip to 'snap-in' to the surface. Thus static mode AFM is almost always done in contact where the overall force is repulsive. Consequently, this technique is typically called 'contact mode'. In contact mode, the force between the tip and the surface is kept constant during scanning by maintaining a constant deflection.

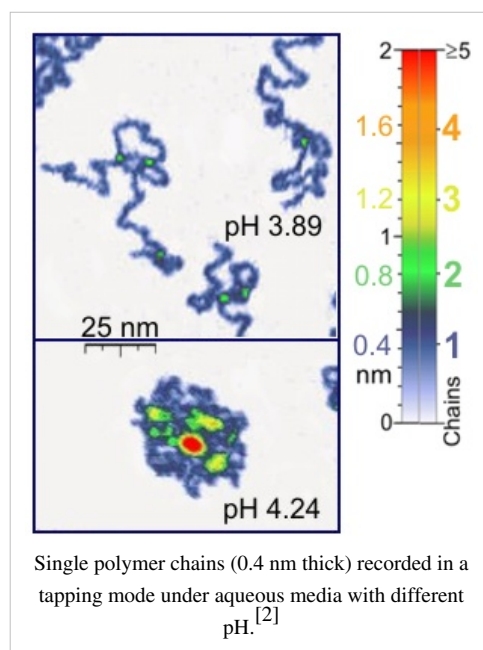
In the dynamic mode, the cantilever is externally oscillated at or close to its fundamental resonance frequency or a harmonic. The oscillation amplitude, phase and resonance frequency are modified by tip-sample interaction forces; these changes in oscillation with respect to the external reference oscillation provide information about the sample's characteristics. Schemes for dynamic mode operation include frequency modulation and the more common amplitude modulation. In frequency modulation, changes in the oscillation frequency provide information about tip-sample interactions. Frequency can be measured with very high sensitivity and thus the frequency modulation mode allows for the use of very stiff cantilevers. Stiff cantilevers provide stability very close to the surface and, as a result, this technique was the first AFM technique to provide true atomic resolution in ultra-high vacuum conditions.^[1]

In amplitude modulation, changes in the oscillation amplitude or phase provide the feedback signal for imaging. In amplitude modulation, changes in the phase of oscillation can be used to discriminate between different types of materials on the surface. Amplitude modulation can be operated either in the non-contact or in the intermittent contact regime. In ambient conditions, most samples develop a liquid meniscus layer. Because of this, keeping the probe tip close enough to the sample for short-range forces to become detectable while preventing the tip from sticking to the surface presents a major hurdle for the non-contact dynamic mode in ambient conditions. Dynamic contact mode (also called intermittent contact or tapping mode) was developed to bypass this problem.^[3] In dynamic contact mode, the cantilever is oscillated such that the separation distance between the cantilever tip and the sample surface is modulated.

Amplitude modulation has also been used in the non-contact regime to image with atomic resolution by using very stiff cantilevers and small amplitudes in an ultra-high vacuum environment.

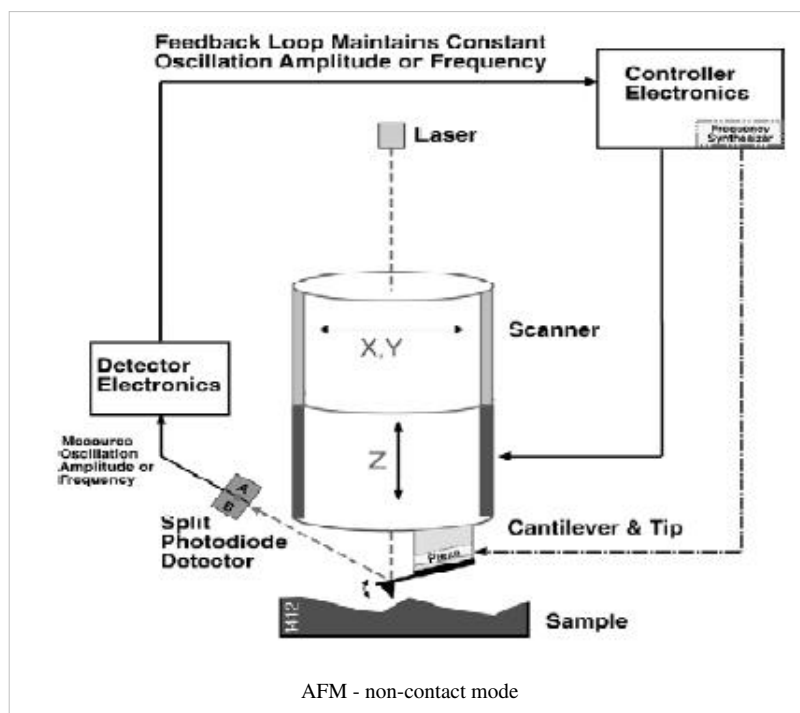
Tapping mode

In *tapping mode*, the cantilever is driven to oscillate up and down at near its resonance frequency by a small piezoelectric element mounted in the AFM tip holder. The amplitude of this oscillation is greater than 10 nm, typically 100 to 200 nm. Due to the interaction of forces acting on the cantilever when the tip comes close to the surface, Van der Waals force or dipole-dipole interaction, electrostatic forces, etc cause the amplitude of this oscillation to decrease as the tip gets closer to the sample. An electronic servo uses the piezoelectric actuator to control the height of the cantilever above the sample. The servo adjusts the height to maintain a set cantilever oscillation amplitude as the cantilever is scanned over the sample. A *tapping AFM* image is therefore produced by imaging the force of the oscillating contacts of the tip with the sample surface. This is an improvement on conventional contact AFM, in which the cantilever just drags across the surface at constant force and can result in surface damage. Tapping mode is gentle enough even for the visualization of supported lipid bilayers or adsorbed single polymer molecules (for instance, 0.4 nm thick chains of synthetic polyelectrolytes) under liquid medium. At the application of proper scanning parameters, the conformation of single molecules remains unchanged for hours.^[2]



Non-contact mode

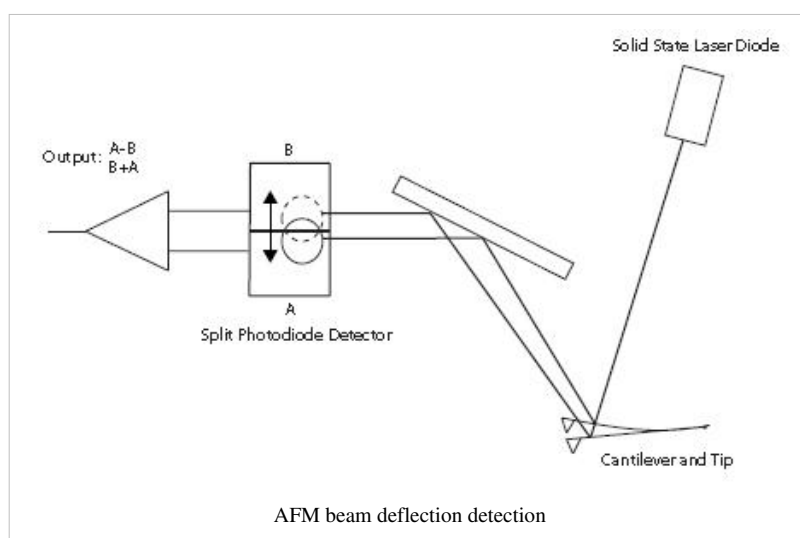
In this mode, the tip of the cantilever does not contact the sample surface. The cantilever is instead oscillated at a frequency slightly above its resonance frequency where the amplitude of oscillation is typically a few nanometers (<10 nm). The van der Waals forces, which are strongest from 1 nm to 10 nm above the surface, or any other long range force which extends above the surface acts to decrease the resonance frequency of the cantilever. This decrease in resonance frequency combined with the feedback loop system maintains a constant oscillation amplitude or frequency by adjusting the average tip-to-sample distance. Measuring the tip-to-sample distance at each (x,y) data point allows the scanning software to construct a topographic image of the sample surface.



Non-contact mode AFM does not suffer from tip or sample degradation effects that are sometimes observed after taking numerous scans with contact AFM. This makes non-contact AFM preferable to contact AFM for measuring soft samples. In the case of rigid samples, contact and non-contact images may look the same. However, if a few monolayers of adsorbed fluid are lying on the surface of a rigid sample, the images may look quite different. An AFM operating in contact mode will penetrate the liquid layer to image the underlying surface, whereas in non-contact mode an AFM will oscillate above the adsorbed fluid layer to image both the liquid and surface.

AFM cantilever deflection measurement

Laser light from a solid state diode is reflected off the back of the cantilever and collected by a position sensitive detector (PSD) consisting of two closely spaced photodiodes whose output signal is collected by a differential amplifier. Angular displacement of cantilever results in one photodiode collecting more light than the other photodiode, producing an output signal (the difference between the photodiode signals normalized by their sum) which is proportional to the deflection of the cantilever. It detects cantilever deflections <10 nm (thermal noise limited). A long beam path (several centimeters) amplifies changes in beam angle.



Force spectroscopy

Another major application of AFM (besides imaging) is force spectroscopy, the direct measurement of tip-sample interaction forces as a function of the gap between the tip and sample (the result of this measurement is called a force-distance curve). For this method, the AFM tip is extended towards and retracted from the surface as the deflection of the cantilever is monitored as a function of piezoelectric displacement. These measurements have been used to measure nanoscale contacts, atomic bonding, Van der Waals forces, and Casimir forces, dissolution forces in liquids and single molecule stretching and rupture forces.^[4] Forces of the order of a few piconewtons can now be routinely measured with a vertical distance resolution of better than 0.1 nanometer. Force spectroscopy can be performed with either static or dynamic modes. In dynamic modes, information about the cantilever vibration is monitored in addition to the static deflection.^[5]

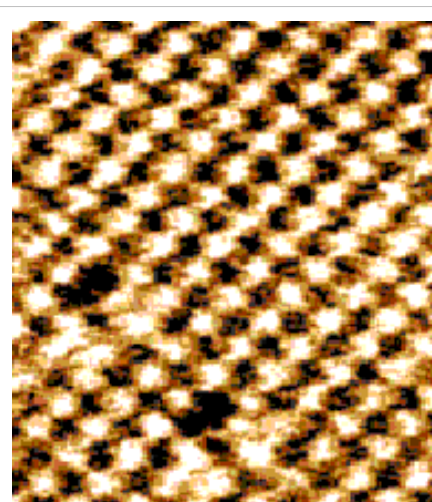
Problems with the technique include no direct measurement of the tip-sample separation and the common need for low stiffness cantilevers which tend to 'snap' to the surface. The snap-in can be reduced by measuring in liquids or by using stiffer cantilevers, but in the latter case a more sensitive deflection sensor is needed. By applying a small dither to the tip, the stiffness (force gradient) of the bond can be measured as well.^[6]

Identification of individual surface atoms

The AFM can be used to image and manipulate atoms and structures on a variety of surfaces. The atom at the apex of the tip "senses" individual atoms on the underlying surface when it forms incipient chemical bonds with each atom. Because these chemical interactions subtly alter the tip's vibration frequency, they can be detected and mapped. This principle was used to distinguish between atoms of silicon, tin and lead on an alloy surface, by comparing these 'atomic fingerprints' to values obtained from large-scale density functional theory (DFT) simulations.^[7]

The trick is to first measure these forces precisely for each type of atom expected in the sample, and then to compare with forces given by DFT simulations. The team found that the tip interacted most strongly with silicon atoms, and interacted 23% and 41% less strongly with tin and lead atoms, respectively. Thus, each different type of atom can be identified in the matrix as the tip is moved across the surface.

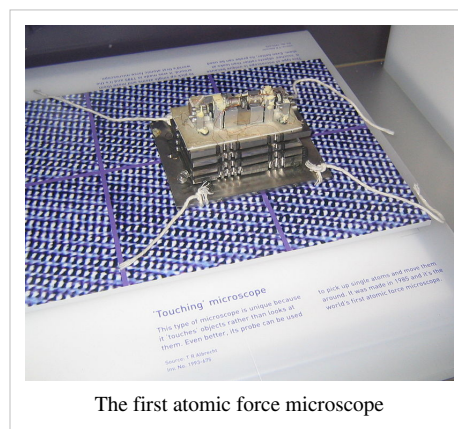
Such a technique has been used now in biology and extended recently to cell biology. Forces corresponding to (i) the unbinding of receptor ligand couples (ii) unfolding of proteins (iii) cell adhesion at single cell scale have been gathered.



The atoms of a sodium chloride crystal viewed with an atomic force microscope

Advantages and disadvantages

The AFM has several advantages over the scanning electron microscope (SEM). Unlike the electron microscope which provides a two-dimensional projection or a two-dimensional image of a sample, the AFM provides a true three-dimensional surface profile. Additionally, samples viewed by AFM do not require any special treatments (such as metal/carbon coatings) that would irreversibly change or damage the sample. While an electron microscope needs an expensive vacuum environment for proper operation, most AFM modes can work perfectly well in ambient air or even a liquid environment. This makes it possible to study biological macromolecules and even living organisms. In principle, AFM can provide higher resolution than SEM. It has been shown to give true atomic resolution in ultra-high vacuum (UHV) and, more recently, in liquid environments. High resolution AFM is comparable in resolution to scanning tunneling microscopy and transmission electron microscopy.



The first atomic force microscope

A disadvantage of AFM compared with the scanning electron microscope (SEM) is the image size. The SEM can image an area on the order of square millimeters with a depth of field on the order of millimeters. The AFM can only image a maximum height on the order of 10-20 micrometers and a maximum scanning area of about 150×150 micrometers. But this is presently being improved, for instance by the use of parallel probes such as used by IBM's "millipede" data storage concept.

Another inconvenience is that an incorrect choice of tip for the required resolution can lead to image artifacts. Traditionally the AFM could not scan images as fast as an SEM, requiring several minutes for a typical scan, while a SEM is capable of scanning at near real-time (although at relatively low quality) after the chamber is evacuated. The relatively slow rate of scanning during AFM imaging often leads to thermal drift in the image^{[8] [9]} making the AFM microscope less suited for measuring accurate distances between topographical features on the image. However, several fast-acting designs^{[10] [11]} were suggested to increase microscope scanning productivity including what is being termed videoAFM (reasonable quality images are being obtained with videoAFM at video rate: faster than the average SEM). To eliminate image distortions induced by thermal drift, several methods^{[8] [9]} were also proposed.

AFM images can also be affected by hysteresis of the piezoelectric material^[12] and cross-talk between the x , y , z axes that may require software enhancement and filtering. Such filtering could "flatten" out real topographical features. However, newer AFMs utilize closed-loop scanners which practically eliminate these problems. Some AFMs also use separated orthogonal scanners (as opposed to a single tube) which also serve to eliminate part of the cross-talk problems.

Due to the nature of AFM probes, they cannot normally measure steep walls or overhangs. Specially made cantilevers and AFMs can be used to modulate the probe sideways as well as up and down (as with dynamic contact and non-contact modes) to measure sidewalls, at the cost of more expensive cantilevers, lower lateral resolution and additional artifacts.

Piezoelectric scanners

AFM scanners are made from piezoelectric material, which expands and contracts proportionally to an applied voltage. Whether they elongate or contract depends upon the polarity of the voltage applied. The scanner is constructed by combining independently operated piezo electrodes for X, Y, and Z into a single tube, forming a scanner which can manipulate samples and probes with extreme precision in 3 dimensions.

Scanners are characterized by their sensitivity which is the ratio of piezo movement to piezo voltage, i.e., by how much the piezo material extends or contracts per applied volt. Because of differences in material or size, the sensitivity varies from scanner to scanner. Sensitivity varies non-linearly with respect to scan size. Piezo scanners exhibit more sensitivity at the end than at the beginning of a scan. This causes the forward and reverse scans to behave differently and display hysteresis^[12] between the two scan directions. This can be corrected by applying a non-linear voltage to the piezo electrodes to cause linear scanner movement and calibrating the scanner accordingly.^[12]

The sensitivity of piezoelectric materials decreases exponentially with time. This causes most of the change in sensitivity to occur in the initial stages of the scanner's life. Piezoelectric scanners are run for approximately 48 hours before they are shipped from the factory so that they are past the point where we can expect large changes in sensitivity. As the scanner ages, the sensitivity will change less with time and the scanner would seldom require recalibration.^[13]

See also

- Chemical force microscopy#Frictional Force Mapping
- Scanning tunneling microscope
- Scanning probe microscopy
- Scanning voltage microscopy
- Surface force apparatus

Further reading

- SPM - Scanning Probe Microscopy Website^[14]
- Atomic Force Microscopy resource library^[15]
- R. W. Carpick and M. Salmeron, Scratching the surface: Fundamental investigations of tribology with atomic force microscopy^[16], Chemical Reviews, vol. 97, iss. 4, pp. 1163-1194 (2007).

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X-ray microscope

An **X-ray microscope** uses electromagnetic radiation in the soft X-ray band to produce images of very small objects. Unlike visible light, X-rays do not reflect or refract easily, and they are invisible to the human eye. Therefore the basic process of an X-ray microscope is to expose film or use a charge-coupled device (CCD) detector to detect X-rays that pass through the specimen. It is a contrast imaging technology using the difference in absorption of soft x-ray in the water window region (wavelength region: 2.3 - 4.4 nm, photon energy region: 0.28 - 0.53 keV) by the carbon atom (main element composing the living cell) and the oxygen atom (main element for water).

Early X-ray microscopes by Paul Kirkpatrick and Albert Baez used grazing-incidence reflective optics to focus the X-rays, which grazed X-rays off parabolic curved mirrors at a very high angle of incidence. An alternative method of focusing X-rays is to use a tiny fresnel zone plate of concentric gold or nickel rings on a silicon dioxide substrate. Sir Lawrence Bragg produced some of the first usable X-ray images with his apparatus in the late 1940's.

In the 1950's Newberry produced a shadow X-ray microscope which placed the specimen between the source and a target plate, this became the basis for the first commercial X-ray microscopes from the General Electric Company.

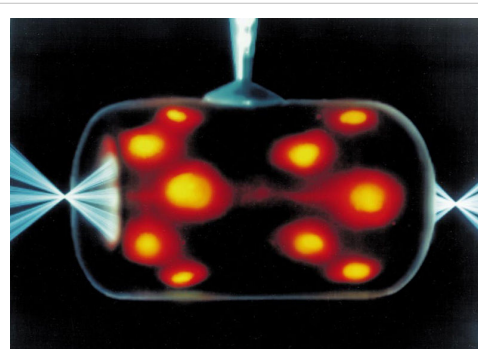
The Advanced Light Source (ALS)[1] in Berkeley CA is home to XM-1 (<http://www.cxro.lbl.gov/BL612/>), a full field soft X-ray microscope operated by the Center for X-ray Optics [2] and dedicated to various applications in modern nanoscience, such as nanomagnetic materials, environmental and materials sciences and biology. XM-1 uses an X-ray lens to focus X-rays on a CCD, in a manner similar to an optical microscope. XM-1 still holds the world record in spatial resolution with Fresnel zone plates down to 15nm and is able to combine high spatial resolution with a sub-100ps time resolution to study e.g. ultrafast spin dynamics.

The ALS is also home to the world's first soft x-ray microscope designed for biological and biomedical research. This new instrument, XM-2 was designed and built by scientists from the National Center for X-ray Tomography (<http://ncxt.lbl.gov>). XM-2 is capable of producing 3-Dimensional tomograms of cells.

Sources of soft X-rays suitable for microscopy, such as synchrotron radiation sources, have fairly low brightness of the required wavelengths, so an alternative method of image formation is scanning transmission soft X-ray microscopy. Here the X-rays are focused to a point and the sample is mechanically scanned through the produced focal spot. At each point the transmitted X-rays are recorded with a detector such as a proportional counter or an avalanche photodiode. This type of Scanning Transmission X-ray Microscope (STXM) was first developed by researchers at Stony Brook University and was employed at the National Synchrotron Light Source at Brookhaven National Laboratory.

The resolution of X-ray microscopy lies between that of the optical microscope and the electron microscope. It has an advantage over conventional electron microscopy in that it can view biological samples in their natural state. Electron microscopy is widely used to obtain images with nanometer level resolution but the relatively thick living cell cannot be observed as the sample has to be chemically fixed, dehydrated, embedded in resin, then sliced ultra thin. However, it should be mentioned that cryo-electron microscopy allows the observation of biological specimens in their hydrated natural state. Until now, resolutions of 30 nanometer are possible using the Fresnel zone plate lens which forms the image using the soft x-rays emitted from a synchrotron. Recently, more researchers have begun to use the soft x-rays emitted from laser-produced plasma rather than synchrotron radiation.

Additionally, X-rays cause fluorescence in most materials, and these emissions can be analyzed to determine the chemical elements of an imaged object. Another use is to generate diffraction patterns, a process used in X-ray crystallography. By analyzing the internal reflections of a diffraction pattern (usually with a computer program), the three-dimensional structure of a crystal can be determined down to the placement of individual atoms within its molecules. X-ray microscopes are sometimes used for these analyses because the samples are too small to be analyzed in any other way.



Indirect drive laser inertial confinement fusion uses a "hohlraum" which is irradiated with laser beam cones from either side on its inner surface to bathe a fusion microcapsule inside with smooth high intensity X-rays.

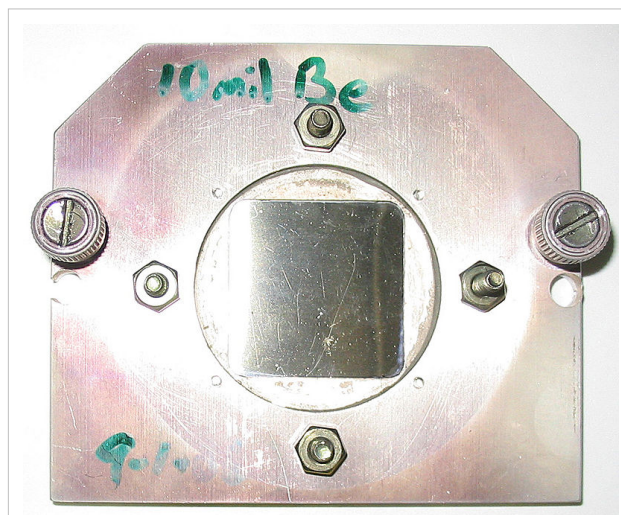
The highest energy X-rays which penetrate the hohlraum can be visualized using an X-ray microscope such as here, where X-radiation is represented in orange/red.

See also

- Synchrotron X-ray tomographic microscopy

External links

- Application of X-ray microscopy in analysis of living hydrated cells ^[19]
- Hard X-ray microbeam experiments with a sputtered-sliced Fresnel zone plate and its applications ^[3]
- Scientific applications of soft x-ray microscopy ^[4]
- X-ray Microscopy in the SEM ^[5]



A square beryllium foil mounted in a steel case to be used as a window between a vacuum chamber and an X-ray microscope. Beryllium, due to its low Z number is highly transparent to X-rays.

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- [3] http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=11972376
- [4] <http://www.cxro.lbl.gov/BL612/index.php?content=research.html>
- [5] http://www.gatan.com/files/PDF/products/XM_502_XuM_Xray_Microscope.pdf

Fluorescence microscope

A **fluorescence microscope** (colloquially synonymous with *epifluorescence microscope*) is an optical microscope used to study properties of organic or inorganic substances using the phenomena of fluorescence and phosphorescence instead of, or in addition to, reflection and absorption.^{[1] [2]}

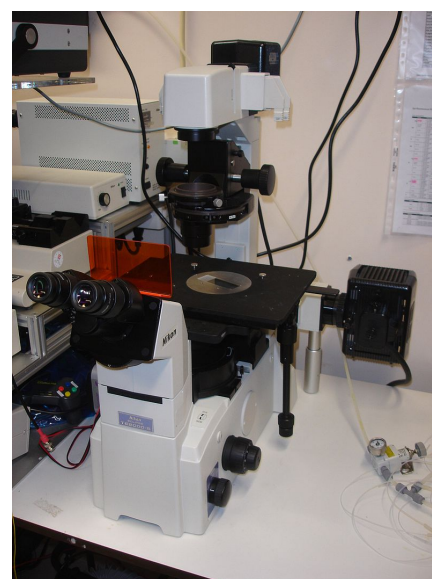


An upright fluorescence microscope (Olympus BX61) with the fluorescent filter cube turret above the objective lenses, coupled with a digital camera.

Technique

In most cases, a component of interest in the specimen can be labeled specifically with a fluorescent molecule called a fluorophore (such as green fluorescent protein (GFP), fluorescein or DyLight 488).^[1] The specimen is illuminated with light of a specific wavelength (or wavelengths) which is absorbed by the fluorophores, causing them to emit light of longer wavelengths (i.e. of a different color than the absorbed light). The illumination light is separated from the much weaker emitted fluorescence through the use of a spectral emission filter. Typical components of a fluorescence microscope are the light source (xenon arc lamp or mercury-vapor lamp), the excitation filter, the dichroic mirror (or dichromatic beamsplitter), and the emission filter (see figure below). The filters and the dichroic are chosen to match the spectral excitation and emission characteristics of the fluorophore used to label the specimen.^[1] In this manner, the distribution of a single fluorophore (color) is imaged at a time. Multi-color images of several types of fluorophores must be composed by combining several single-color images.^[1]

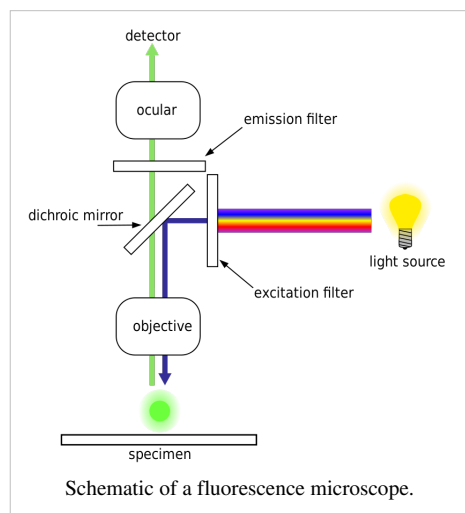
Most fluorescence microscopes in use are epifluorescence microscopes (i.e. excitation and observation of the fluorescence are from above (*epi*–) the specimen). These microscopes have become an important part in the field of biology, opening the doors for more advanced microscope designs, such as the confocal microscope and the total internal reflection fluorescence microscope (TIRF).



An inverted fluorescence microscope (Nikon TE2000) with the fluorescent filter cube turret below the stage. Note the orange plate that allows the user to look at the sample while protecting his eyes from the excitation UV light.

Fluorophores lose their ability to fluoresce as they are illuminated in a process called photobleaching. Special care must be taken to prevent photobleaching through the use of more robust fluorophores, by minimizing illumination, or by introducing a scavenger system to reduce the rate of photobleaching.

Epifluorescence microscopy



Epifluorescence microscopy is a method of fluorescence microscopy that is widely used in life sciences. The excitatory light is passed from above (or, for inverted microscopes, from below), through the objective lens and then onto the specimen instead of passing it first through the specimen. The fluorescence in the specimen gives rise to emitted light which is focused to the detector by the same objective that is used for the excitation. Since most of the excitatory light is transmitted through the specimen, only reflected excitatory light reaches the objective together with the emitted light and this method therefore gives an improved signal to noise ratio. An additional filter between the objective and the detector can filter out the remaining excitation light from fluorescent light. A common use in biology is to apply fluorescent or fluorochrome stains to the specimen in order to image distributions of proteins or other molecules of interest.

Improvements and sub-diffraction techniques

The nature of light limits the size of the spot to which light can be focused. According to the diffraction limit a focused light distribution cannot be made smaller than approximately half of the wavelength of the used light. Uncovered in the 19th century by Ernst Abbe this has been a barrier of the achievable resolution of fluorescence light microscopes for a long time. While resolution is denoted by the ability to discern different objects of the same kind, localizing or tracking of single particles have been performed with a precision much below the diffraction limit.

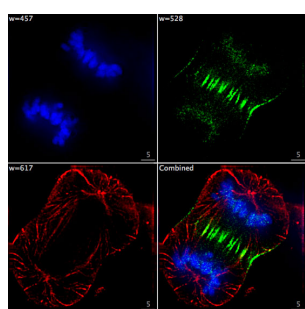
Several improvements in microscopy techniques have been invented in the 20th century and have resulted in increased resolution and contrast to some extent. However they did not overcome the diffraction limit. Among them are the confocal microscope using additional point-like illumination or structured illumination^[3] which can be seen as a parallelized extension of the confocal technique. Also 4Pi microscopy which is maximizing the amount of available focusing directions by using two opposing objective lenses or Multi-photon microscopy using redshifted light and multi-photon excitation.

The first technique to really achieve a sub-diffraction resolution was STED microscopy, proposed only in 1994 by Stefan Hell. This method and all techniques following the RESOLFT concept rely on a strong non-linear interaction between light and fluorescing molecules. The molecules are driven strongly between distinguishable molecular states at each specific location, so that finally light can be emitted at only a small fraction of space, hence an increased resolution.

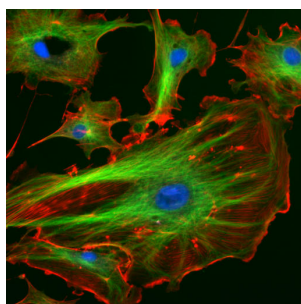
Alternatively, the advent of photoactivated localization microscopy could achieve similar results by relying on blinking or switching of single molecules, where the fraction of fluorescing molecules is very small at each time. This stochastic response of molecules on the applied light corresponds also to a highly nonlinear interaction, leading to subdiffraction resolution.^[4]

Using these subdiffraction techniques is possible with many standard fluorescent dyes like GFP, Alexa dyes or fluorescein molecules.

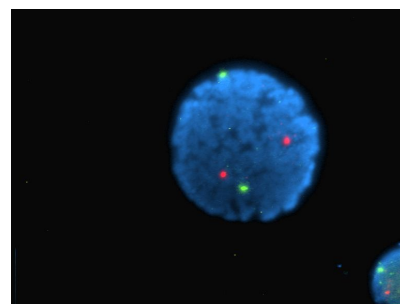
Gallery



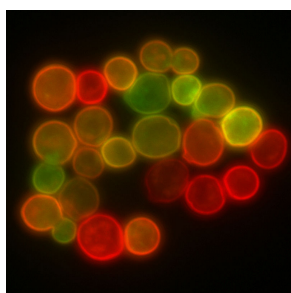
Epifluorescent imaging of the three components in a dividing human cancer cell. DNA is stained blue, a protein called INCENP is green, and the microtubules are red. Each fluorophore is imaged separately using a different combination of excitation and emission filters, and the images are captured sequentially using a digital CCD camera, then overlaid to give a complete image.



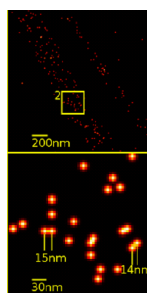
Endothelial cells under the microscope. Nuclei are stained blue with DAPI, microtubules are marked green by an antibody bound to FITC and actin filaments are labeled red with phalloidin bound to TRITC. Bovine pulmonary artery endothelial (BPAE) cells



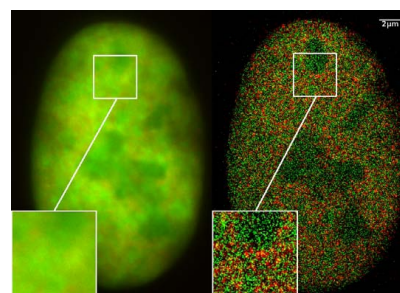
Human lymphocyte nucleus stained with DAPI with chromosome 13 (green) and 21 (red) centromere probes hybridized (Fluorescent in situ hybridization (FISH))



Yeast cell membrane visualized by some membrane proteins fused with RFP and GFP fluorescent markers. Imposition of light from both of markers results in yellow color.



Single YFP molecule detection in a human cancer cell. Typical distance measurements in the 15 nm range (5 nm standard deviation)



Co-localization microscopy (2CLM) with GFP and RFP fusion proteins (nucleus of a bone cancer cell) 120.000 localized molecules in a wide-field area ($470 \mu\text{m}^2$)

See also

- Microscope
- Mercury-vapor lamp, Xenon arc lamp
- Stokes shift

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External links

- Fluorophores.org (<http://www.fluorophores.org>) - Database of fluorescent dyes.
-

Fluorescence correlation spectroscopy

Fluorescence correlation spectroscopy (FCS) is a common technique used by physicists, chemists, and biologists to experimentally characterize the dynamics of fluorescent species (e.g. single fluorescent dye molecules in nanostructured materials, autofluorescent proteins in living cells, etc.). Although the name indicates a specific link to fluorescence, the method is used today also for exploring other forms of luminescence (like reflections, luminescence from gold-beads or quantum dots or phosphorescent species). The word "spectroscopy" in the name differs from common usage, in which a spectrum is generally understood to be a frequency spectrum. The autocorrelation is a genuine form of spectrum, however: It is the time-spectrum generated from the power spectrum (via inverse Fourier transform).

Commonly, FCS is employed in the context of optical microscopy, in particular confocal or two-photon microscopy. In these techniques light is focused on a sample and the measured fluorescence intensity fluctuations (due to diffusion, physical or chemical reactions, aggregation, etc.) are analyzed using the temporal autocorrelation. Because the measured property is essentially related to the magnitude and/or the amount of fluctuations, there is an optimum measurement regime at the level when individual species enter or exit the observation volume (or turn on and off in the volume). When too many entities are measured at the same time the overall fluctuations are small in comparison to the total signal and may not be resolvable – in the other direction, if the individual fluctuation-events are too sparse in time, one measurement may take prohibitively too long. FCS is in a way the fluorescent counterpart to dynamic light scattering, which uses coherent light scattering, instead of (incoherent) fluorescence.

When an appropriate model is known, FCS can be used to obtain quantitative information such as

- diffusion coefficients
- hydrodynamic radii
- average concentrations
- kinetic chemical reaction rates
- singlet-triplet dynamics

Because fluorescent markers come in a variety of colors and can be specifically bound to a particular molecule (e.g. proteins, polymers, metal-complexes, etc.), it is possible to study the behavior of individual molecules (in rapid succession in composite solutions). With the development of sensitive detectors such as avalanche photodiodes the detection of the fluorescence signal coming from individual molecules in highly dilute samples has become practical. With this emerged the possibility to conduct FCS experiments in a wide variety of specimens, ranging from materials science to biology. The advent of engineered cells with genetically tagged proteins (like green fluorescent protein) has made FCS a common tool for studying molecular dynamics in living cells.

History

Signal-correlation techniques were first experimentally applied to fluorescence in 1972 by Magde, Elson, and Webb^[1], who are therefore commonly credited as the "inventors" of FCS. The technique was further developed in a group of papers by these and other authors soon after, establishing the theoretical foundations and types of applications.^{[2] [3] [4]} See Thompson (1991)^[5] for a review of that period.

Beginning in 1993^[6], a number of improvements in the measurement techniques—notably using confocal microscopy, and then two-photon microscopy—to better define the measurement volume and reject background—greatly improved the signal-to-noise ratio and allowed single molecule sensitivity.^{[7] [8]} Since then, there has been a renewed interest in FCS, and as of August 2007 there have been over 3,000 papers using FCS found in Web of Science. See Krichevsky and Bonnet^[9] for a recent review. In addition, there has been a flurry of activity extending FCS in various ways, for instance to laser scanning and spinning-disk confocal microscopy (from a stationary, single point measurement), in using cross-correlation (FCCS) between two fluorescent channels instead

of autocorrelation, and in using Förster Resonance Energy Transfer (FRET) instead of fluorescence.

Typical FCS setup

The typical FCS setup consists of a laser line (wavelengths ranging typically from 405–633 nm (cw), and from 690–1100 nm (pulsed)), which is reflected into a microscope objective by a dichroic mirror. The laser beam is focused in the sample, which contains fluorescent particles (molecules) in such high dilution, that only a few are within the focal spot (usually 1–100 molecules in one fL). When the particles cross the focal volume, they fluoresce. This light is collected by the same objective and, because it is red-shifted with respect to the excitation light it passes the dichroic mirror reaching a detector, typically a photomultiplier tube or avalanche photodiode detector. The resulting electronic signal can be stored either directly as an intensity versus time trace to be analyzed at a later point, or computed to generate the autocorrelation directly (which requires special acquisition cards). The FCS curve by itself only represents a time-spectrum. Conclusions on physical phenomena have to be extracted from there with appropriate models. The parameters of interest are found after fitting the autocorrelation curve to modeled functional forms.^[10]

The measurement volume

The measurement volume is a convolution of illumination (excitation) and detection geometries, which result from the optical elements involved. The resulting volume is described mathematically by the point spread function (or PSF), it is essentially the image of a point source. The PSF is often described as an ellipsoid (with unsharp boundaries) of few hundred nanometers in focus diameter, and almost one micrometre along the optical axis. The shape varies significantly (and has a large impact on the resulting FCS curves) depending on the quality of the optical elements (it is crucial to avoid astigmatism and to check the real shape of the PSF on the instrument). In the case of confocal microscopy, and for small pinholes (around one Airy unit), the PSF is well approximated by Gaussians:

$$PSF(r, z) = I_0 e^{-2r^2/\omega_{xy}^2} e^{-2z^2/\omega_z^2}$$

where I_0 is the peak intensity, r and z are radial and axial position, and ω_{xy} and ω_z are the radial and axial radii, and $\omega_z > \omega_{xy}$. This Gaussian form is assumed in deriving the functional form of the autocorrelation.

Typically ω_{xy} is 200–300 nm, and ω_z is **2–6** times larger.^[11] One common way of calibrating the measurement volume parameters is to perform FCS on a species with known diffusion coefficient and concentration (see below). Diffusion coefficients for common fluorophores in water are given in a later section.

The Gaussian approximation works to varying degrees depending on the optical details, and corrections can sometimes be applied to offset the errors in approximation.^[12]

Autocorrelation function

The (temporal) autocorrelation function is the correlation of a time series with itself shifted by time τ , as a function of τ :

$$G(\tau) = \frac{\langle \delta I(t) \delta I(t + \tau) \rangle}{\langle I(t) \rangle^2} = \frac{\langle I(t) I(t + \tau) \rangle}{\langle I(t) \rangle^2} - 1$$

where $\delta I(t) = I(t) - \langle I(t) \rangle$ is the deviation from the mean intensity. The normalization (denominator) here is the most commonly used for FCS, because then the correlation at $\tau = 0$, $G(0)$, is related to the average number of particles in the measurement volume.

Interpreting the autocorrelation function

To extract quantities of interest, the autocorrelation data can be fitted, typically using a nonlinear least squares algorithm. The fit's functional form depends on the type of dynamics (and the optical geometry in question).

Normal diffusion

The fluorescent particles used in FCS are small and thus experience thermal motions in solution. The simplest FCS experiment is thus normal 3D diffusion, for which the autocorrelation is:

$$G(\tau) = G(0) \frac{1}{(1 + (\tau/\tau_D)) (1 + a^{-2}(\tau/\tau_D))^{1/2}} + G(\infty)$$

where $a = \omega_z/\omega_{xy}$ is the ratio of axial to radial e^{-2} radii of the measurement volume, and τ_D is the characteristic residence time. This form was derived assuming a Gaussian measurement volume. Typically, the fit would have three free parameters-- $G(0)$, $G(\infty)$, and τ_D --from which the diffusion coefficient and fluorophore concentration can be obtained.

With the normalization used in the previous section, $G(0)$ gives the mean number of diffusers in the volume $\langle N \rangle$, or equivalently—with knowledge of the observation volume size—the mean concentration:

$$G(0) = \frac{1}{\langle N \rangle} = \frac{1}{V_{\text{eff}} \langle C \rangle},$$

where the effective volume is found from integrating the Gaussian form of the measurement volume and is given by:

$$V_{\text{eff}} = \pi^{3/2} \omega_{xy}^2 \omega_z.$$

τ_D gives the diffusion coefficient:

$$D = \omega_{xy}^2 / 4\tau_D.$$

Anomalous diffusion

If the diffusing particles are hindered by obstacles or pushed by a force (molecular motors, flow, etc.) the dynamics is often not sufficiently well-described by the normal diffusion model, where the mean squared displacement (MSD) grows linearly with time. Instead the diffusion may be better described as anomalous diffusion, where the temporal dependence of the MSD is non-linear as in the power-law:

$$MSD = 6D_a t^\alpha$$

where D_a is an anomalous diffusion coefficient. "Anomalous diffusion" commonly refers only to this very generic model, and not the many other possibilities that might be described as anomalous. Also, a power law is, in a strict sense, the expected form only for a narrow range of rigorously defined systems, for instance when the distribution of obstacles is fractal. Nonetheless a power law can be a useful approximation for a wider range of systems.

The FCS autocorrelation function for anomalous diffusion is:

$$G(\tau) = G(0) \frac{1}{(1 + (\tau/\tau_D)^\alpha) (1 + a^{-2}(\tau/\tau_D)^\alpha)^{1/2}} + G(\infty),$$

where the anomalous exponent α is the same as above, and becomes a free parameter in the fitting.

Using FCS, the anomalous exponent has been shown to be an indication of the degree of molecular crowding (it is less than one and smaller for greater degrees of crowding)^[13].

Polydisperse diffusion

If there are diffusing particles with different sizes (diffusion coefficients), it is common to fit to a function that is the sum of single component forms:

$$G(\tau) = G(0) \sum_i \frac{\alpha_i}{(1 + (\tau/\tau_{D,i})) (1 + a^{-2}(\tau/\tau_{D,i}))^{1/2}} + G(\infty)$$

where the sum is over the number different sizes of particle, indexed by i , and α_i gives the weighting, which is related to the quantum yield and concentration of each type. This introduces new parameters, which makes the fitting more difficult as a higher dimensional space must be searched. Nonlinear least square fitting typically becomes unstable with even a small number of $\tau_{D,i}$ s. A more robust fitting scheme, especially useful for polydisperse samples, is the Maximum Entropy Method^[14].

Diffusion with flow

With diffusion together with a uniform flow with velocity v in the lateral direction, the autocorrelation is^[15]:

$$G(\tau) = G(0) \frac{1}{(1 + (\tau/\tau_D)) (1 + a^{-2}(\tau/\tau_D))^{1/2}} \times \exp[-(\tau/\tau_v)^2 \times \frac{1}{1 + \tau/\tau_D}] + G(\infty)$$

where $\tau_v = \omega_{xy}/v$ is the average residence time if there is only a flow (no diffusion).

Chemical relaxation

A wide range of possible FCS experiments involve chemical reactions that continually fluctuate from equilibrium because of thermal motions (and then "relax"). In contrast to diffusion, which is also a relaxation process, the fluctuations cause changes between states of different energies. One very simple system showing chemical relaxation would be a stationary binding site in the measurement volume, where particles only produce signal when bound (e.g. by FRET, or if the diffusion time is much faster than the sampling interval). In this case the autocorrelation is:

$$G(\tau) = G(0) \exp(-\tau/\tau_B) + G(\infty)$$

where

$$\tau_B = (k_{on} + k_{off})^{-1}$$

is the relaxation time and depends on the reaction kinetics (on and off rates), and:

$$G(0) = \frac{1}{\langle N \rangle} \frac{k_{on}}{k_{off}} = \frac{1}{\langle N \rangle} K$$

is related to the equilibrium constant K .

Most systems with chemical relaxation also show measureable diffusion as well, and the autocorrelation function will depend on the details of the system. If the diffusion and chemical reaction are decoupled, the combined autocorrelation is the product of the chemical and diffusive autocorrelations.

Triplet state correction

The autocorrelations above assume that the fluctuations are not due to changes in the fluorescent properties of the particles. However, for the majority of (bio)organic fluorophores--e.g. green fluorescent protein, rhodamine, Cy3 and Alexa Fluor dyes--some fraction of illuminated particles are excited to a triplet state (or other non-radiative decaying states) and then do not emit photons for a characteristic relaxation time τ_F . Typically τ_F is on the order of microseconds, which is usually smaller than the dynamics of interest (e.g. τ_D) but large enough to be measured. A multiplicative term is added to the autocorrelation account for the triplet state. For normal diffusion:

$$G(\tau) = G(0) \frac{1 - F + F e^{-\tau/\tau_F}}{1 - F} \frac{1}{(1 + (\tau/\tau_{D,i})) (1 + a^{-2}(\tau/\tau_{D,i}))^{1/2}} + G(\infty)$$

where F is the fraction of particles that have entered the triplet state and τ_F is the corresponding triplet state relaxation time. If the dynamics of interest are much slower than the triplet state relaxation, the short time component of the autocorrelation can simply be truncated and the triplet term is unnecessary.

Common fluorescent probes

The fluorescent species used in FCS is typically a biomolecule of interest that has been tagged with a fluorophore (using immunohistochemistry for instance), or is a naked fluorophore that is used to probe some environment of interest (e.g. the cytoskeleton of a cell). The following table gives diffusion coefficients of some common fluorophores in water at room temperature, and their excitation wavelengths.

Fluorescent dye	D ($\times 10^{-10} \text{ m}^2 \text{ s}^{-1}$)	Excitation wavelength (nm)	Reference
Rhodamine 6G	2.8, 3.0, 4.14 ± 0.05 @ 25.00 °C	514	[16] [17] [18]
Rhodamine 110	2.7	488	[19]
Tetramethyl rhodamine	2.6	543	
Cy3	2.8	543	
Cy5	2.5, 3.7 ± 0.15 @ 25.00 °C	633	[20] [21]
carboxyfluorescein	3.2	488	
Alexa-488	1.96	488	[22]
Atto655-maleimide	4.07 ± 0.1 @ 25.00 °C	663	[23]
Atto655-carboxylicacid	4.26 ± 0.08 @ 25.00 °C	663	[24]
2', 7'-difluorofluorescein (Oregon Green488)	4.11 ± 0.06 @ 25.00 °C	498	[25]

Variations of FCS

FCS almost always refers to the single point, single channel, temporal autocorrelation measurement, although the term "fluorescence correlation spectroscopy" out of its historical scientific context implies no such restriction. FCS has been extended in a number of variations by different researchers, with each extension generating another name (usually an acronym).

Fluorescence cross-correlation spectroscopy (FCCS)

FCS is sometimes used to study molecular interactions using differences in diffusion times (e.g. the product of an association reaction will be larger and thus have larger diffusion times than the reactants individually); however, FCS is relatively insensitive to molecular mass as can be seen from the following equation relating molecular mass to the diffusion time of globular particles (e.g. proteins):

$$\tau_D = \frac{3\pi\omega_{xy}^2\eta}{2kT}(M)^{1/3}$$

where η is the viscosity of the sample and M is the molecular mass of the fluorescent species. In practice, the diffusion times need to be sufficiently different—a factor of at least **1.6**—which means the molecular masses must differ by a factor of **4**.^[26] Dual color fluorescence cross-correlation spectroscopy (FCCS) measures interactions by cross-correlating two or more fluorescent channels (one channel for each reactant), which distinguishes interactions more sensitively than FCS, particularly when the mass change in the reaction is small.

Brightness analysis methods (N&B,^[27] PCH,^[28] FIDA,^[29] Cumulant Analysis^[30])

Fluorescence cross correlation spectroscopy overcomes the weak dependence of diffusion rate on molecular mass by looking at multicolor coincidence. What about homo-interactions? The solution lies in brightness analysis. These methods use the heterogeneity in the intensity distribution of fluorescence to measure the molecular brightness of different species in a sample. Since dimers will contain twice the number of fluorescent labels as monomers, their molecular brightness will be approximately double that of monomers. As a result, the relative brightness is sensitive a measure of oligomerization. The average molecular brightness ($\langle \epsilon \rangle$) is related to the variance (σ^2) and the average intensity ($\langle I \rangle$) as follows:^[31]

$$\langle \epsilon \rangle = \frac{\sigma^2 - \langle I \rangle}{\langle I \rangle} = \sum_i f_i \epsilon_i$$

Here f_i and ϵ_i are the fractional intensity and molecular brightness, respectively, of species i .

Two- and three- photon FCS excitation

Several advantages in both spatial resolution and minimizing photodamage/photobleaching in organic and/or biological samples are obtained by two-photon or three-photon excitation FCS^{[32] [33] [34] [35] [36]}.

FRET-FCS

Another FCS based approach to studying molecular interactions uses fluorescence resonance energy transfer (FRET) instead of fluorescence, and is called FRET-FCS.^[37] With FRET, there are two types of probes, as with FCCS; however, there is only one channel and light is only detected when the two probes are very close—close enough to ensure an interaction. The FRET signal is weaker than with fluorescence, but has the advantage that there is only signal during a reaction (aside from autofluorescence).

Image correlation spectroscopy (ICS)

When the motion is slow (in biology, for example, diffusion in a membrane), getting adequate statistics from a single-point FCS experiment may take a prohibitively long time. More data can be obtained by performing the experiment in multiple spatial points in parallel, using a laser scanning confocal microscope. This approach has been called Image Correlation Spectroscopy (ICS)^[38]. The measurements can then be averaged together.

Another variation of ICS performs a spatial autocorrelation on images, which gives information about the concentration of particles^[39]. The correlation is then averaged in time.

A natural extension of the temporal and spatial correlation versions is spatio-temporal ICS (STICS)^[40]. In STICS there is no explicit averaging in space or time (only the averaging inherent in correlation). In systems with non-isotropic motion (e.g. directed flow, asymmetric diffusion), STICS can extract the directional information. A variation that is closely related to STICS (by the Fourier transform) is k -space Image Correlation Spectroscopy (kICS).^[41]

There are cross-correlation versions of ICS as well.^[38]

Scanning FCS variations

Some variations of FCS are only applicable to serial scanning laser microscopes. Image Correlation Spectroscopy and its variations all were implemented on a scanning confocal or scanning two photon microscope, but transfer to other microscopes, like a spinning disk confocal microscope. Raster ICS (RICS)^[42], and position sensitive FCS (PSFCS)^[43] incorporate the time delay between parts of the image scan into the analysis. Also, low dimensional scans (e.g. a circular ring)^[44]—only possible on a scanning system—can access time scales between single point and full image measurements. Scanning path has also been made to adaptively follow particles.^[45]

Spinning disk FCS, and spatial mapping

Any of the image correlation spectroscopy methods can also be performed on a spinning disk confocal microscope, which in practice can obtain faster imaging speeds compared to a laser scanning confocal microscope. This approach has recently been applied to diffusion in a spatially varying complex environment, producing a pixel resolution map of a diffusion coefficient.^[46] The spatial mapping of diffusion with FCS has subsequently been extended to the TIRF system.^[47] Spatial mapping of dynamics using correlation techniques had been applied before, but only at sparse points^[48] or at coarse resolution^[40].

Total internal reflection FCS

Total internal reflection fluorescence (TIRF) is a microscopy approach that is only sensitive to a thin layer near the surface of a coverslip, which greatly minimizes background fluorescence. FCS has been extended to that type of microscope, and is called TIR-FCS^[49]. Because the fluorescence intensity in TIRF falls off exponentially with distance from the coverslip (instead of as a Gaussian with a confocal), the autocorrelation function is different.

Other fluorescent dynamical approaches

There are two main non-correlation alternatives to FCS that are widely used to study the dynamics of fluorescent species.

Fluorescence recovery after photobleaching (FRAP)

In FRAP, a region is briefly exposed to intense light, irreversibly photobleaching fluorophores, and the fluorescence recovery due to diffusion of nearby (non-bleached) fluorophores is imaged. A primary advantage of FRAP over FCS is the ease of interpreting qualitative experiments common in cell biology. Differences between cell lines, or regions of a cell, or before and after application of drug, can often be characterized by simple inspection of movies. FCS experiments require a level of processing and are more sensitive to potentially confounding influences like: rotational diffusion, vibrations, photobleaching, dependence on illumination and fluorescence color, inadequate statistics, etc. It is much easier to change the measurement volume in FRAP, which allows greater control. In practice, the volumes are typically larger than in FCS. While FRAP experiments are typically more qualitative, some researchers are studying FRAP quantitatively and including binding dynamics.^[50] A disadvantage of FRAP in cell biology is the free radical perturbation of the cell caused by the photobleaching. It is also less versatile, as it cannot measure concentration or rotational diffusion, or co-localization. FRAP requires a significantly higher concentration of fluorophores than FCS.

Particle tracking

In particle tracking, the trajectories of a set of particles are measured, typically by applying particle tracking algorithms to movies.^[51] Particle tracking has the advantage that all the dynamical information is maintained in the measurement, unlike FCS where correlation averages the dynamics to a single smooth curve. The advantage is apparent in systems showing complex diffusion, where directly computing the mean squared displacement allows straightforward comparison to normal or power law diffusion. To apply particle tracking, the particles have to be distinguishable and thus at lower concentration than required of FCS. Also, particle tracking is more sensitive to noise, which can sometimes affect the results unpredictably.

See also

- Confocal microscopy
- Fluorescence cross-correlation spectroscopy, FCCS
- FRET
- Dynamic light scattering
- Diffusion coefficient

External links

- Single-molecule spectroscopic methods ^[52]
- FCS Classroom ^[53]
- Stowers Institute FCS Tutorial ^[54]
- Cell Migration Consortium FCS Tutorial ^[55]

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Fluorescence cross-correlation spectroscopy

Fluorescence cross-correlation spectroscopy (FCCS) was introduced by Eigen and Rigler in 1994 and experimentally realized by Schwille in 1997. It extends the fluorescence correlation spectroscopy (FCS) procedure by introducing high sensitivity for distinguishing fluorescent particles which have a similar diffusion coefficient. FCCS uses two species which are independently labelled with two spectrally separated fluorescent probes. These fluorescent probes are excited and detected by two different laser light sources and detectors commonly known as green and red respectively. Both laser light beams are focused into the sample and tuned so that they overlap to form a superimposed confocal observation volume.

The normalized cross-correlation function is defined for two fluorescent species G and R which are independent green, G and red, R channels as follows:

$$G_{GR}(\tau) = 1 + \frac{\langle \delta I_G(t) \delta I_R(t + \tau) \rangle}{\langle I_G(t) \rangle \langle I_R(t) \rangle} = \frac{\langle I_G(t) I_R(t + \tau) \rangle}{\langle I_G(t) \rangle \langle I_R(t) \rangle}$$

where differential fluorescent signals δI_G at a specific time, t and δI_R at a delay time, τ later is correlated with each other.

Modeling

Cross-correlation curves are modeled according to a slightly more complicated mathematical function than applied in FCS. First of all, the effective superimposed observation volume in which the G and R channels form a single observation volume, $V_{eff,GR}$ in the solution:

$$V_{eff,GR} = \pi^{3/2} (\omega_{xy,G}^2 + \omega_{xy,R}^2) (\omega_{z,G}^2 + \omega_{z,R}^2)^{1/2} / 2^{3/2}$$

where $\omega_{xy,G}^2$ and $\omega_{xy,R}^2$ are radial parameters and $\omega_{z,G}$ and $\omega_{z,R}$ are the axial parameters for the G and R channels respectively.

The diffusion time, $\tau_{D,GR}$ for a doubly (G and R) fluorescent species is therefore described as follows:

$$\tau_{D,GR} = \frac{\omega_{xy,G}^2 + \omega_{xy,R}^2}{8D_{GR}}$$

where D_{GR} is the diffusion coefficient of the doubly fluorescent particle.

The cross-correlation curve generated from diffusing doubly labelled fluorescent particles can be modelled in separate channels as follows:

$$G_G(\tau) = 1 + \frac{(\langle C_G \rangle Diff_k(\tau) + \langle C_{GR} \rangle Diff_k(\tau))}{V_{eff,GR}(\langle C_G \rangle + \langle C_{GR} \rangle)^2}$$

$$G_R(\tau) = 1 + \frac{(\langle C_R \rangle Diff_k(\tau) + \langle C_{GR} \rangle Diff_k(\tau))}{V_{eff,GR}(\langle C_R \rangle + \langle C_{GR} \rangle)^2}$$

In the ideal case, the cross-correlation function is proportional to the concentration of the doubly labeled fluorescent complex:

$$G_{GR}(\tau) = 1 + \frac{\langle C_{GR} \rangle Diff_{GR}(\tau)}{V_{eff}(\langle C_G \rangle + \langle C_{GR} \rangle)(\langle C_R \rangle + \langle C_{GR} \rangle)}$$

$$\text{with } Diff_k(\tau) = \frac{1}{(1 + \frac{\tau}{\tau_{D,i}})(1 + a^{-2}(\frac{\tau}{\tau_{D,i}})^{1/2})}$$

Contrary to FCS, the intercept of the cross-correlation curve does not yield information about the doubly labelled fluorescent particles in solution.

See also

- Fluorescence correlation spectroscopy
- Dynamic light scattering
- Fluorescence spectroscopy
- Diffusion coefficient

External links

- FCS Classroom^[53]

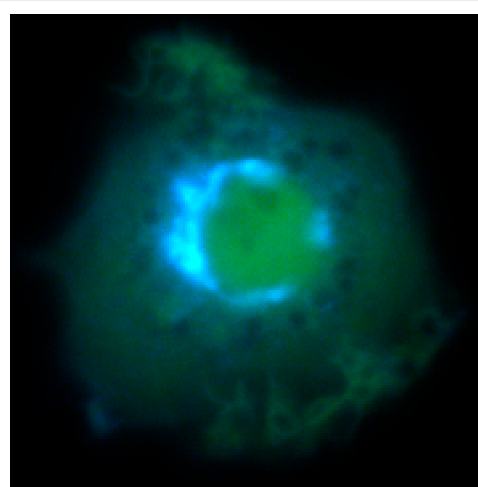
Förster resonance energy transfer

Förster resonance energy transfer (abbreviated **FRET**), also known as **fluorescence resonance energy transfer**, **resonance energy transfer (RET)** or **electronic energy transfer (EET)**, is a mechanism describing energy transfer between two chromophores.

A donor chromophore, initially in its electronic excited state, may transfer energy to an acceptor chromophore (in proximity, typically less than 10 nm) through nonradiative dipole–dipole coupling. This mechanism is termed "Förster resonance energy transfer" and is named after the German scientist Theodor Förster.^[2] When both chromophores are fluorescent, the term "fluorescence resonance energy transfer" is often used instead, although the energy is not actually transferred by fluorescence.^[3]^[4] In order to avoid an erroneous interpretation of the

phenomenon that (even when occurring between two fluorescent chromophores) is always a nonradiative transfer of energy, the name "Förster resonance energy transfer" is preferred to "fluorescence resonance energy transfer" – although the latter enjoys common usage in scientific literature. FRET is analogous

to near field communication, in that the radius of interaction is much smaller than the wavelength of light emitted. In the near field region, the excited chromophore emits a virtual photon that is instantly absorbed by a receiving chromophore. These virtual photons are undetectable, since their existence violates the conservation of energy and momentum, and hence FRET is known as a *radiationless* mechanism. From quantum electrodynamical calculations, it is determined that radiationless (FRET) and radiative energy transfer are the short- and long-range asymptotes of a single unified mechanism.^[5]^[6]



Fluorescently-labeled guanosine 5'-triphosphate hydrolase ARF reveals the protein's localization in the Golgi apparatus of a living macrophage. FRET studies revealed ARF activation in the Golgi and in the formation of phagosomes.^[1]

Theoretical basis

The FRET efficiency (E) is the quantum yield of the energy transfer transition, *i.e.* the fraction of energy transfer event occurring per donor excitation event:

$$E = \frac{k_{ET}}{k_f + k_{ET} + \sum k_i}$$

where k_{ET} is the rate of energy transfer, k_f the radiative decay rate and the k_i are the rate constants of any other de-excitation pathway.

The FRET efficiency depends on many parameters that can be grouped as follows:

- The distance between the donor and the acceptor
- The spectral overlap of the donor emission spectrum and the acceptor absorption spectrum.
- The relative orientation of the donor emission dipole moment and the acceptor absorption dipole moment.

E depends on the donor-to-acceptor separation distance r with an inverse 6th power law due to the dipole-dipole coupling mechanism:

$$E = \frac{1}{1 + (r/R_0)^6}$$

with R_0 being the Förster distance of this pair of donor and acceptor, *i.e.* the distance at which the energy transfer efficiency is 50%. The Förster distance depends on the overlap integral of the donor emission spectrum with the acceptor absorption spectrum and their mutual molecular orientation as expressed by the following equation:

$$R_0^6 = \frac{9 Q_0 (\ln 10) \kappa^2 J}{128 \pi^5 n^4 N_A}$$

where Q_0 is the fluorescence quantum yield of the donor in the absence of the acceptor, κ^2 is the dipole orientation factor, n is the refractive index of the medium, N_A is Avogadro's number, and J is the spectral overlap integral calculated as

$$J = \int f_D(\lambda) \epsilon_A(\lambda) \lambda^4 d\lambda$$

where f_D is the normalized donor emission spectrum, and ϵ_A is the acceptor molar extinction coefficient. $\kappa^2 = 2/3$ is often assumed. This value is obtained when both dyes are freely rotating and can be considered to be isotropically oriented during the excited state lifetime. If either dye is fixed or not free to rotate, then $\kappa^2 = 2/3$ will not be a valid assumption. In most cases, however, even modest reorientation of the dyes results in enough orientational averaging that $\kappa^2 = 2/3$ does not result in a large error in the estimated energy transfer distance due to the sixth power dependence of R_0 on κ^2 . Even when κ^2 is quite different from $2/3$ the error can be associated with a shift in R_0 and thus determinations of changes in relative distance for a particular system are still valid. Fluorescent proteins do not reorient on a timescale that is faster than their fluorescence lifetime. In this case $0 \leq \kappa^2 \leq 4$.

The FRET efficiency relates to the quantum yield and the fluorescence lifetime of the donor molecule as follows:

$$E = 1 - \tau'_D / \tau_D$$

where τ'_D and τ_D are the donor fluorescence lifetimes in the presence and absence of an acceptor, respectively, or as

$$E = 1 - F'_D / F_D$$

where F'_D and F_D are the donor fluorescence intensities with and without an acceptor, respectively.

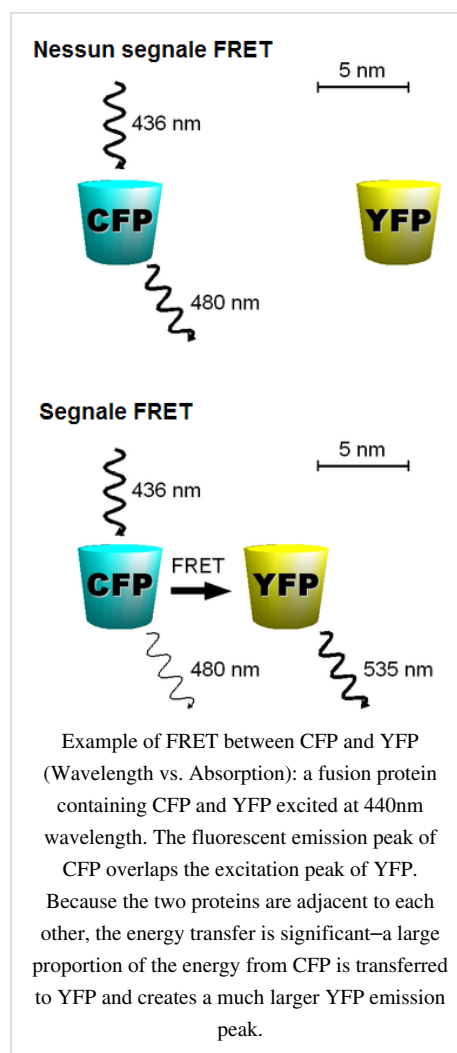
Methods

In fluorescence microscopy, fluorescence confocal laser scanning microscopy, as well as in molecular biology, FRET is a useful tool to quantify molecular dynamics in biophysics and biochemistry, such as protein-protein interactions, protein-DNA interactions, and protein conformational changes. For monitoring the complex formation between two molecules, one of them is labeled with a donor and the other with an acceptor, and these fluorophore-labeled molecules are mixed. When they are dissociated, the donor emission is detected upon the donor excitation. On the other hand, when the donor and acceptor are in proximity (1-10 nm) due to the interaction of the two molecules, the acceptor emission is predominantly observed because of the intermolecular FRET from the donor to the acceptor. For monitoring protein conformational changes, the target protein is labeled with a donor and an acceptor at two loci. When a twist or bend of the protein brings the change in the distance or relative orientation of the donor and acceptor, FRET change is observed. If a molecular interaction or a protein conformational change is dependent on ligand binding, this FRET technique is applicable to fluorescent indicators for the ligand detection.

FRET studies are scalable: the extent of energy transfer is often quantified from the milliliter scale of cuvette-based experiments to the femtoliter scale of microscopy-based experiments. This quantification can be based directly (sensitized emission method) on detecting two emission channels under two different excitation conditions (primarily donor and primarily acceptor). However, for robustness reasons, FRET quantification is most often based on measuring changes in fluorescence intensity or fluorescence lifetime upon changing the experimental conditions (e.g. a microscope image of donor emission is taken with the acceptor being present. The acceptor is then bleached, such that it is incapable of accepting energy transfer and another donor emission image is acquired. A pixel-based quantification using the second equation in the theory section above is then possible.) An alternative way of temporarily deactivating the acceptor is based on its fluorescence saturation. Exploiting polarisation characteristics of light, a FRET quantification is also possible with only a single camera exposure.

CFP-YFP pairs

The most popular FRET pair for biological use is a cyan fluorescent protein (CFP) - yellow fluorescent protein (YFP) pair. Both are color variants of green fluorescent protein (GFP). While labeling with organic fluorescent dyes requires troublesome processes of purification, chemical modification, and intracellular injection of a host protein, GFP variants can be easily attached to a host protein by genetic engineering. By virtue of GFP variants, the use of FRET techniques for biological research is becoming more and more popular.



BRET

A limitation of FRET is the requirement for external illumination to initiate the fluorescence transfer, which can lead to background noise in the results from direct excitation of the acceptor or to photobleaching. To avoid this drawback, Bioluminescence Resonance Energy Transfer (or **BRET**) has been developed. This technique uses a bioluminescent luciferase (typically the luciferase from *Renilla reniformis*) rather than CFP to produce an initial photon emission compatible with YFP.

FRET and BRET are also the common tools in the study of biochemical reaction kinetics and molecular motors.

Photobleaching FRET

FRET efficiencies can also be inferred from the photobleaching rates of the donor in the presence and absence of an acceptor. This method can be performed on most fluorescence microscopes; one simply shines the excitation light (of a frequency that will excite the donor but not the acceptor significantly) on specimens with and without the acceptor fluorophore and monitors the donor fluorescence (typically separated from acceptor fluorescence using a bandpass filter) over time. The timescale is that of photobleaching, which is seconds to minutes, with fluorescence in each curve being given by

$$(\text{background}) + (\text{constant}) * e^{-(\text{time})/\tau_{\text{pb}}}$$

where τ_{pb} is the photobleaching decay time constant and depends on whether the acceptor is present or not. Since photobleaching consists in the permanent inactivation of excited fluorophores, resonance energy transfer from an excited donor to an acceptor fluorophore prevents the photobleaching of that donor fluorophore, and thus high FRET efficiency leads to a longer photobleaching decay time constant:

$$E = 1 - \tau_{\text{pb}}/\tau'_{\text{pb}}$$

where τ'_{pb} and τ_{pb} are the photobleaching decay time constants of the donor in the presence and in the absence of the acceptor, respectively. (Notice that the fraction is the reciprocal of that used for lifetime measurements). This technique was introduced by Jovin in 1989.^[7] Its use of an entire curve of points to extract the time constants can give it accuracy advantages over the other methods. Also, the fact that time measurements are over seconds rather than nanoseconds makes it easier than fluorescence lifetime measurements, and because photobleaching decay rates do not generally depend on donor concentration (unless acceptor saturation is an issue), the careful control of concentrations needed for intensity measurements is not needed. It is, however, important to keep the illumination the same for the with- and without-acceptor measurements, as photobleaching increases markedly with more intense incident light.

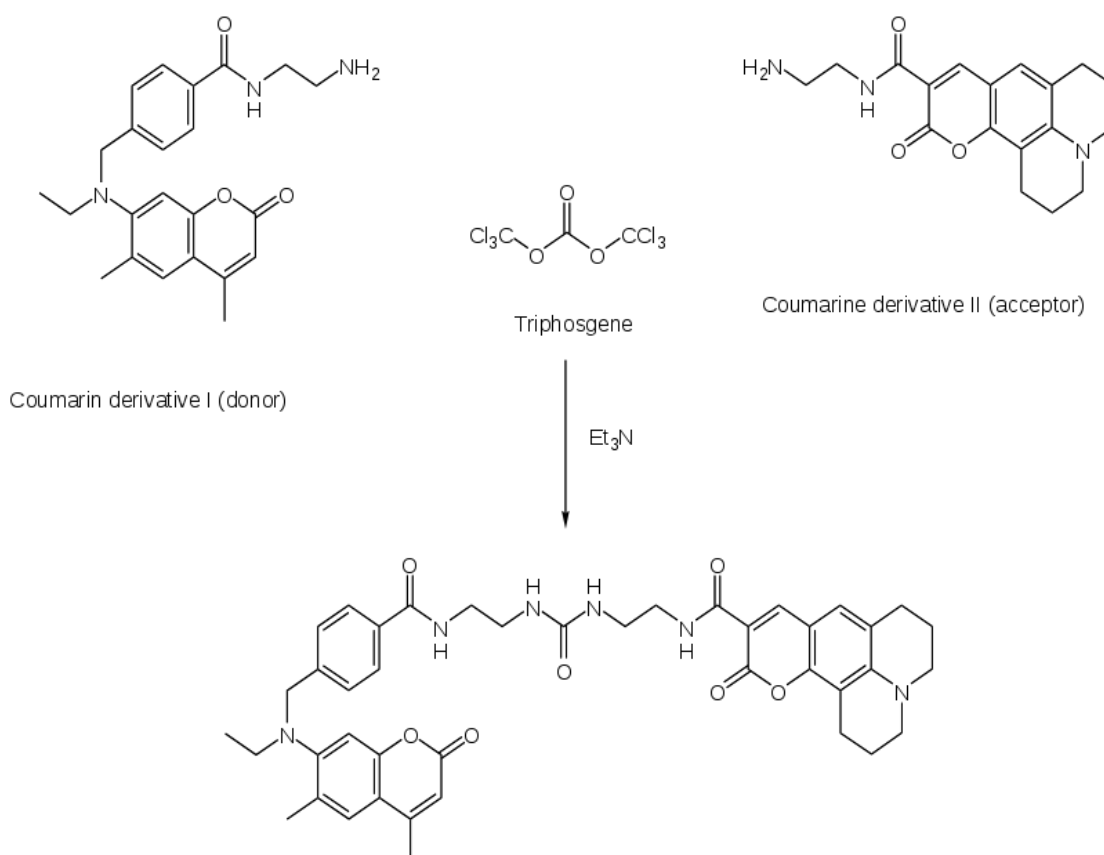
Other methods

A different, but related, mechanism is Dexter Electron Transfer.

An alternative method to detecting protein-protein proximity is the bimolecular fluorescence complementation (BiFC) where two halves of a YFP are fused to a protein. When these two halves meet they form a fluorophore after about 60 s - 1 hr.^[8]

Applications

FRET has been applied in an experimental method for the detection of phosgene. In it, phosgene or rather triphosgene as a safe substitute serves as a linker between an acceptor and a donor coumarine (forming urea groups).^[9] The presence of phosgene is detected at $5 \times 10^{-5} \text{ M}$ with a typical FRET emission at 464 nm.



FRET is also used to study lipid rafts in cell membranes.^[10]

See also

- Resonant energy transfer is used for remotely powering equipment such as smart cards
- Fluorescence principles / energy tranfert (FRET): light emitted upon excitation by illumination at a shorter wavelenght
- Bioluminescence principles / energy tranfert (BRET): light emitted by a chemical enzymatic reaction (Luminol/Peroxidase, Luciferin/Luciferase, Coelenterazine/Aequorin)

External links

- Browser-based calculator to find the critical distance and FRET efficiency with known spectral overlap^[11]
- FCS^{[12] [13] [14] [15] [16]}

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Neutron scattering

Neutron scattering encompasses all scientific techniques whereby the deflection of neutron radiation is used as a scientific probe. Neutrons readily interact with atomic nuclei and magnetic fields from unpaired electrons, making a useful probe of both structure and magnetic order. Neutron Scattering falls into two basic categories - elastic and inelastic. Elastic scattering is when a neutron interacts with a nucleus or electronic magnetic field but does not leave it in an excited state, meaning the emitted neutron has the same energy as the injected neutron. Scattering processes that involve an energetic excitation or relaxation by the neutron are inelastic: the injected neutron's energy is used or increased to create an excitation or by absorbing the excess energy from a relaxation, and consequently the emitted neutron's energy is reduced or increased respectively.

For several good reasons, moderated neutrons provide an ideal tool for the study of almost all forms of condensed matter. Firstly, they are readily produced at a nuclear research reactor or a spallation source. Normally in such processes neutrons are however produced with much higher energies than are needed. Therefore moderators are generally used which slow the neutrons down and therefore produce wavelengths that are comparable to the atomic spacing in solids and liquids, and kinetic energies that are comparable to those of dynamic processes in materials. Moderators can be made from aluminium and filled with liquid hydrogen (for very long wavelength neutrons) or liquid methane (for shorter wavelength neutrons). Fluxes of $10^7/\text{s}$ - $10^8/\text{s}$ are not atypical in most neutron sources from any given moderator.

The neutrons cause pronounced interference and energy transfer effects in scattering experiments. Unlike an x-ray photon with a similar wavelength, which interacts with the electron cloud surrounding the nucleus, neutrons interact with the nucleus itself. Because the neutron is an electrically neutral particle, it is deeply penetrating, and is therefore more able to probe the bulk material. Consequently, it enables the use of a wide range of sample environments that are difficult to use with synchrotron x-ray sources. It also has the advantage that the cross sections for interaction do not increase with atomic number as they do with radiation from a synchrotron x-ray source. Thus neutrons can be used to analyse materials with low atomic numbers like proteins and surfactants. This can be done at synchrotron sources but very high intensities are needed which may cause the structures to change. Moreover, the nucleus provides a very short range, isotropic potential varying randomly from isotope to isotope, making it possible to tune the nuclear scattering contrast to suit the experiment:

The neutron has an additional advantage over the x-ray photon in the study of condensed matter. It readily interacts with internal magnetic fields in the sample. In fact, the strength of the magnetic scattering signal is often very similar to that of the nuclear scattering signal in many materials, which allows the simultaneous exploration of both nuclear

and magnetic structure. Because the neutron scattering amplitude can be measured in absolute units, both the structural and magnetic properties as measured by neutrons can be compared quantitatively with the results of other characterisation techniques.

See also

- Neutron diffraction
 - Small angle neutron scattering
 - Neutron Reflectometry
- Inelastic neutron scattering
 - neutron triple-axis spectrometry
 - neutron time-of-flight scattering
 - neutron backscattering
 - neutron spin echo
 - neutron resonance spin echo
- Neutron scattering facilities

External links

- Neutron Scattering - A primer ^[1] (LANL-hosted black and white version ^[2]) - An introductory article written by Roger Pynn (Los Alamos National Laboratory)
- Podcast Interview with two ILL scientists about neutron science/scattering at the ILL ^[3]

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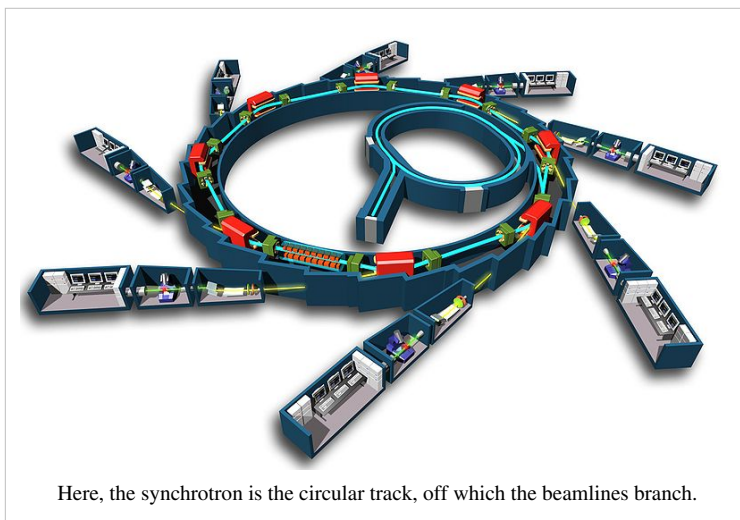
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Synchrotron

A **synchrotron** is a particular type of cyclic particle accelerator in which the magnetic field (to turn the particles so they circulate) and the electric field (to accelerate the particles) are carefully synchronized with the travelling particle beam. The proton synchrotron was originally conceived by Sir Marcus Oliphant (1901–2000)^[1]. The honour of being the first to publish the idea went to Vladimir Veksler (1907–1966), and the first electron synchrotron was constructed by Edwin McMillan (1907–1991).



Here, the synchrotron is the circular track, off which the beamlines branch.

Characteristics

While a cyclotron uses a constant magnetic field and a constant-frequency applied electric field (one of these is varied in the synchrocyclotron), both of these fields are varied in the synchrotron. By increasing these parameters appropriately as the particles gain energy, their path can be held constant as they are accelerated. This allows the vacuum chamber for the particles to be a large thin torus. In reality it is easier to use some straight sections between the bending magnets and some bent sections within the magnets giving the torus the shape of a round-cornered polygon. A path of large effective radius may thus be constructed using simple straight and curved pipe segments, unlike the disc-shaped chamber of the cyclotron type devices. The shape also allows and requires the use of multiple magnets to bend the particle beams. Straight sections are required at spacings around a ring for both radiofrequency cavities, and in third generation setups space is allowed for insertion of energy extraction devices such as wigglers and undulators.

The maximum energy that a cyclic accelerator can impart is typically limited by the strength of the magnetic field(s) and the minimum radius (maximum curvature) of the particle path.

In a cyclotron the maximum radius is quite limited as the particles start at the center and spiral outward, thus the entire path must be a self-supporting disc-shaped evacuated chamber. Since the radius is limited, the power of the machine becomes limited by the strength of the magnetic field. In the case of an ordinary electromagnet the field strength is limited by the saturation of the core (when all

magnetic domains are aligned the field may not be further increased to any practical extent). The arrangement of the single pair of magnets the full width of the device also limits the economic size of the device.

Synchrotrons overcome these limitations, using a narrow beam pipe which can be surrounded by much smaller and more tightly focusing magnets. The ability of this device to accelerate particles is limited by the fact that the particles



The interior of the Australian Synchrotron facility. Dominating the image is the storage ring, showing the optical diagnostic beamline at front right. In the middle of the storage ring is the booster synchrotron and linac

must be charged to be accelerated at all, but charged particles under acceleration emit photons (light), thereby losing energy. The limiting beam energy is reached when the energy lost to the lateral acceleration required to maintain the beam path in a circle equals the energy added each cycle. More powerful accelerators are built by using large radius paths and by using more numerous and more powerful microwave cavities to accelerate the particle beam between corners. Lighter particles (such as electrons) lose a larger fraction of their energy when turning. Practically speaking, the energy of electron/positron accelerators is limited by this radiation loss, while it does not play a significant role in the dynamics of proton or ion accelerators. The energy of those is limited strictly by the strength of magnets and by the cost.

Design and operation

Particles are injected into the main ring at substantial energies by either a linear accelerator or by an intermediate synchrotron which is in turn fed by a linear accelerator. The "linac" is in turn fed by particles accelerated to intermediate energy by a simple high voltage power supply, typically a Cockcroft-Walton generator.

Starting from an appropriate initial value determined by the injection velocity the magnetic field is then increased. The particles pass through an electrostatic accelerator driven by a high alternating voltage. At particle speeds not close to the speed of light the frequency of the accelerating voltage can be made roughly proportional to the current in the bending magnets. A finer control of the frequency is performed by a servo loop which responds to the detection of the passing of the traveling group of particles. At particle speeds approaching light speed the frequency becomes more nearly constant, while the current in the bending magnets continues to increase. The maximum energy that can be applied to the particles (for a given ring size and magnet count) is determined by the saturation of the cores of the bending magnets (the point at which increasing current does not produce additional magnetic field). One way to obtain additional power is to make the torus larger and add additional bending magnets. This allows the amount of particle redirection at saturation to be less and so the particles can be more energetic. Another means of obtaining higher power is to use superconducting magnets, these not being limited by core saturation.

Large synchrotrons

One of the early large synchrotrons, now retired, is the Bevatron, constructed in 1950 at the Lawrence Berkeley Laboratory. The name of this proton accelerator comes from its power, in the range of 6.3 GeV (then called BeV for billion electron volts; the name predates the adoption of the SI prefix giga-). A number of heavy elements, unseen in the natural world, were first created with this machine. This site is also the location of one of the first large bubble chambers used to examine the results of the atomic collisions produced here.



Modern industrial-scale synchrotrons can be very large (here, Soleil near Paris)

Another early large synchrotron is the Cosmotron built at Brookhaven National Laboratory which reached 3.3 GeV in 1953.^[2]

Until August 2008, the highest energy synchrotron in the world was the Tevatron, at the Fermi National Accelerator Laboratory, in the United States. It accelerates protons and antiprotons to slightly less than 1 TeV of kinetic energy and collides them together. The Large Hadron Collider (LHC), which has been built at the European Laboratory for High Energy Physics (CERN), has roughly seven times this energy (so proton-proton collisions occur at roughly 14

TeV). It is housed in the 27 km tunnel which formerly housed the Large Electron Positron (LEP) collider, so it will maintain the claim as the largest scientific device ever built. The LHC will also accelerate heavy ions (such as lead) up to an energy of 1.15 PeV.

The largest device of this type seriously proposed was the Superconducting Super Collider (SSC), which was to be built in the United States. This design, like others, used superconducting magnets which allow more intense magnetic fields to be created without the limitations of core saturation. While construction was begun, the project was cancelled in 1994, citing excessive budget overruns — this was due to naïve cost estimation and economic management issues rather than any basic engineering flaws. It can also be argued that the end of the Cold War resulted in a change of scientific funding priorities that contributed to its ultimate cancellation. While there is still potential for yet more powerful proton and heavy particle cyclic accelerators, it appears that the next step up in electron beam energy must avoid losses due to synchrotron radiation. This will require a return to the linear accelerator, but with devices significantly longer than those currently in use. There is at present a major effort to design and build the International Linear Collider (ILC), which will consist of two opposing linear accelerators, one for electrons and one for positrons. These will collide at a total center of mass energy of 0.5 TeV.

However, synchrotron radiation also has a wide range of applications (see synchrotron light) and many 2nd and 3rd generation synchrotrons have been built especially to harness it. The largest of those 3rd generation synchrotron light sources are the European Synchrotron Radiation Facility (ESRF) in Grenoble, France, the Advanced Photon Source (APS) near Chicago, USA, and SPring-8 in Japan, accelerating electrons up to 6, 7 and 8 GeV, respectively.

Synchrotrons which are useful for cutting edge research are large machines, costing tens or hundreds of millions of dollars to construct, and each beamline (there may be 20 to 50 at a large synchrotron) costs another two or three million dollars on average. These installations are mostly built by the science funding agencies of governments of developed countries, or by collaborations between several countries in a region, and operated as infrastructure facilities available to scientists from universities and research organisations throughout the country, region, or world. More compact models, however, have been developed, such as the Compact Light Source.

List of installations

Synchrotron	Location & Country	Energy (GeV)	Circumference (m)	Commissioned	Decommissioned
Advanced Photon Source (APS)	Argonne National Laboratory, USA	7.0	1104	1995	
ALBA	Cerdanyola del Vallès near Barcelona, Spain	3	270	2010	
ISIS	Rutherford Appleton Laboratory, UK	0.8	163	1985	
Australian Synchrotron	Melbourne, Australia	3	216	2006	
ANKA	Karlsruhe Institute of Technology, Germany	2.5	110.4	2000	
LNLS	Campinas, Brazil	1.37	93.2	1997	
SESAME	Allaan, Jordan	2.5	125	Under Design	
Bevatron	Lawrence Berkeley Laboratory, USA	6	114	1954	1993
Advanced Light Source	Lawrence Berkeley Laboratory, USA	1.9	196.8	1993	
Cosmotron	Brookhaven National Laboratory, USA	3	72	1953	1968
National Synchrotron Light Source	Brookhaven National Laboratory, USA	2.8	170	1982	
Nimrod	Rutherford Appleton Laboratory, UK	7		1957	1978
Alternating Gradient Synchrotron (AGS)	Brookhaven National Laboratory, USA	33	800	1960	

Stanford Synchrotron Radiation Lightsource	SLAC National Accelerator Laboratory, USA	3	234	1973	
Synchrotron Radiation Center (SRC)	Madison, USA	1	121	1968	
Cornell High Energy Synchrotron Source (CHESS)	Cornell University, USA	5.5	768	1979	
Soleil	Paris, France	3	354	2006	
Shanghai Synchrotron Radiation Facility (SSRF)	Shanghai, China	3.5	432	2007	
Proton Synchrotron	CERN, Switzerland	28	628.3	1959	
Tevatron	Fermi National Accelerator Laboratory, USA	1000	6300	1983	
Swiss Light Source	Paul Scherrer Institute, Switzerland	2.8	288	2001	
Large Hadron Collider (LHC)	CERN, Switzerland	7000	26659	2008	
BESSY II	Helmholtz-Zentrum Berlin in Berlin, Germany	1.7	240	1998	
European Synchrotron Radiation Facility (ESRF)	Grenoble, France	6	844	1992	
MAX-I	MAX-lab, Sweden	0.55	30	1986	
MAX-II	MAX-lab, Sweden	1.5	90	1997	
MAX-III	MAX-lab, Sweden	0.7	36	2008	
ELETTRA	Trieste, Italy	2-2.4	260	1993	
Synchrotron Radiation Source	Daresbury Laboratory, UK	2	96	1980	2008
ASTRID	Aarhus University, Denmark	0.58	40	1991	
Diamond Light Source	Oxfordshire, UK	3	561.6	2006	
DORIS III	DESY, Germany	4.5	289	1980	
PETRA II	DESY, Germany	12	2304	1995	2007
Canadian Light Source	University of Saskatchewan, Canada	2.9	171	2002	
SPring-8	RIKEN, Japan	8	1436	1997	
Taiwanese National Synchrotron Radiation Research Center	Hsinchu Science Park, Taiwan	3.3	518.4	2008	
Synchrotron Light Research Institute (SLRI)	Nakhon Ratchasima, Thailand	1.2	81.4	2004	
Indus 1	Raja Ramanna Centre for Advanced Technology, Indore, India	0.45		1999	
Indus 2	Raja Ramanna Centre for Advanced Technology, Indore, India	2.5	36	2005	
Synchrophasotron	JINR, Dubna, USSR	10	180	1957	2005
U-70 synchrotron	IHEP, Protvino, USSR	70		1967	
CAMD	LSU, Louisiana, US	1.5	-	-	
PLS	PAL, Pohang, Korea	2.5	280.56	1994	

- Note: in the case of colliders, the quoted energy is often double what is shown here. The above table shows the energy of one beam but if two opposing beams collide head on, the centre of mass energy is double the beam energy shown.

Applications

- Life sciences: protein and large molecule crystallography
- LIGA based microfabrication
- Drug discovery and research
- "Burning" computer chip designs into metal wafers
- Studying molecule shapes and protein crystals
- Analyzing chemicals to determine their composition
- Observing the reaction of living cells to drugs
- Inorganic material crystallography and microanalysis
- Fluorescence studies
- Semiconductor material analysis and structural studies
- Geological material analysis
- Medical imaging
- Proton therapy to treat some forms of cancer

See also

- List of synchrotron radiation facilities
- Synchrotron X-ray tomographic microscopy
- Energy amplifier
- Superconducting Radio Frequency

External links

- Canadian Light Source ^[3]
- Australian Synchrotron ^[4]
- Diamond UK Synchrotron ^[5]
- Lightsources.org ^[6]
- CERN Large Hadron Collider ^[7]
- Synchrotron Light Sources of the World ^[8]
- A Miniature Synchrotron: ^[9] room-size synchrotron offers scientists a new way to perform high-quality x-ray experiments in their own labs, *Technology Review*, February 04, 2008
- Brazilian Synchrotron Light Laboratory ^[10]
- Podcast interview ^[11] with a scientist at the European Synchrotron Radiation Facility

References

- [1] Nature 407, 468 (28 September 2000) (<http://www.nature.com/nature/journal/v407/n6803/full/407468a0.html>).
- [2] The Cosmotron (<http://www.bnl.gov/bnlweb/history/cosmotron.asp>)
- [3] <http://www.lightsource.ca>
- [4] <http://www.synchrotron.org.au>
- [5] <http://www.diamond.ac.uk>
- [6] <http://www.lightsources.org/cms/>
- [7] <http://lhc-new-homepage.web.cern.ch/lhc-new-homepage>
- [8] http://www-als.lbl.gov/als/synchrotron_sources.html
- [9] <http://www.technologyreview.com/Biotech/20149/>
- [10] <http://www.lnls.br/lnls/cgi/cgilua.exe/sys/start.htm?UserActiveTemplate=lnls%5F2007%5Fenglish&tpl=home>
- [11] <http://omegataupodcast.net/2009/03/28/11-synchrotron-radiation-science-at-esrf/>

ISIS neutron source

ISIS is a pulsed neutron and muon source. It is situated at the Rutherford Appleton Laboratory in Oxfordshire, United Kingdom and is part of the Science and Technology Facilities Council. It uses the techniques muon spectroscopy and neutron scattering to probe the structure and dynamics of condensed matter on a microscopic scale ranging from the subatomic to the macromolecular.

Hundreds of experiments are performed annually at ISIS by visiting researchers from around the world, in diverse science areas including physics, chemistry, materials engineering, earth sciences, biology and archaeology.

Neutrons and muons

Neutrons are uncharged constituents of atoms and penetrate materials well, deflecting only from the nuclei of atoms. The statistical accumulation of deflected neutrons at different positions beyond the sample can be used to find the structure of a

material, and the loss or gain of energy by neutrons can reveal the dynamic behaviour of parts of a sample, for example diffusive processes in solids. At ISIS the neutrons are created by accelerating 'bunches' of protons in a synchrotron, then colliding these with a heavy tantalum metal target, under a constant cooling load to dissipate the heat from the 160 kW proton beam. The tantalum atoms slough off neutrons, and these are channelled through guides, or beamlines, to about 20 instruments, individually optimised for the study of different types of matter. The target station and most of the instruments are set in a large hall. The penetrating neutrons are a dangerous form of radiation so the target and beamlines are heavily shielded with concrete.

ISIS produces muons by colliding a fraction of the proton beam with a graphite target, producing pions which decay rapidly into muons, delivered in a spin-polarised beam to sample stations.



ISIS experimental hall for Target Station 1

Science at ISIS

ISIS is administered and operated by the Science and Technology Facilities Council (previously CCLRC). Experimental time is open to academic users from funding countries and is applied for through a twice-yearly 'call for proposals'. Research allocation, or 'beam-time', is allotted to applicants via a peer-review process. Users and their parent institutions do not pay for

the running costs of the facility, which are as much as £11,000 per instrument per day. Their transport and living costs are also refunded whilst carrying out the experiment. Most users stay in Ridgeway House, a hotel near the site, or at Cosener's House, an STFC-run conference centre in Abingdon. Over 600 experiments by 1600 users are completed every year.

A large number of support staff operate the facility, aid users, and carry out research, the control room is staffed 24 hours a day, every day of the year. Instrument scientists oversee the running of each instrument and liaise with users, and other divisions provide sample environment, data analysis and computing expertise, maintain the accelerator, and run education programmes.

Among the important and pioneering work carried out was the discovery of the structure of high-temperature superconductors and the solid phase of buckminsterfullerene.

Construction for a second target station started in 2003, and the first neutrons were delivered to the target on December 14, 2007^[1]. It will use low-energy neutrons to study soft condensed matter, biological systems, advanced composites and nanomaterials. To supply the extra protons for this, the accelerator is being upgraded.

History and background of ISIS

The source was approved in 1977 for the RAL site on the Harwell campus and recycled components from earlier UK science programmes including the accelerator hall which had previously been occupied by the Nimrod accelerator. The first beam was produced in 1984, and the facility was formally opened by the then Prime Minister Margaret Thatcher in October 1985.^[2]

The name ISIS is not an acronym: it refers to the Ancient Egyptian goddess and the local name for the River Thames. The name was selected for the official opening of the facility in 1985, prior to this it was known as the SNS, or Spallation Neutron Source. The name was considered appropriate as Isis was a goddess who could restore life to the dead, and ISIS made use of equipment previously constructed for the Nimrod and Nina accelerators^[3].



Another view of the ISIS experimental hall for Target Station 1

External links

- ISIS facility ^[4]
- ISIS Second Target Station ^[5]
- The Science and Technology Facilities Council ^[6]

References

- [1] ISIS Second Target Station Project (<http://ts-2.isis.rl.ac.uk/>)
- [2] Linacs at the Rutherford Appleton Laboratory (<http://epubs.cclrc.ac.uk/bitstream/692/linacplahistory.pdf>)
- [3] Explanation of the name of ISIS (<http://www.isis.rl.ac.uk/aboutIsis/index.htm>)
- [4] <http://www.isis.stfc.ac.uk/>
- [5] <http://www.isis.stfc.ac.uk/about-isis/target-station-2/>
- [6] <http://www.stfc.ac.uk>

Geographical coordinates: 51°34′18″N 1°19′12″W

Nuclear Medicine Applications

Nuclear medicine

Nuclear medicine is a branch or specialty of medicine and medical imaging that uses radioactive isotopes (radionuclides) and relies on the process of radioactive decay in the diagnosis and treatment of disease.

In nuclear medicine procedures, radionuclides are combined with other chemical compounds or pharmaceuticals to form radiopharmaceuticals. These radiopharmaceuticals, once administered to the patient, can localize to specific organs or cellular receptors. This property of radiopharmaceuticals allows nuclear medicine the ability to image the extent of a disease-process in the body, based on the cellular function and physiology, rather than relying on physical changes in the tissue anatomy. In some diseases nuclear medicine studies can identify medical problems at an earlier stage than other diagnostic tests.

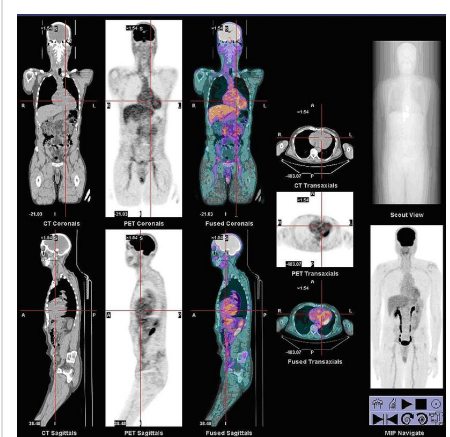
Treatment of disease, based on metabolism or uptake or binding of a ligand, may also be accomplished, similar to other areas of pharmacology. However, radiopharmaceuticals rely on the tissue-destructive power of short-range ionizing radiation.

Description of the field

In nuclear medicine imaging, radiopharmaceuticals are taken internally, for example intravenously or orally. Then, external detectors (gamma cameras) capture and form images from the radiation emitted by the radiopharmaceuticals. This process is unlike a diagnostic X-ray where external radiation is passed through the body to form an image.

There are several techniques of diagnostic nuclear medicine. *Scintigraphy* ("scint") is the use of internal radioisotopes to create two-dimensional^[1] images. *SPECT* is a 3D tomographic technique that uses gamma camera data from many projections and can be reconstructed in different planes. *Positron emission tomography* (PET) uses coincidence detection to image functional processes.

Nuclear medicine tests differ from most other imaging modalities in that diagnostic tests primarily show the physiological function of the system being investigated as opposed to traditional anatomical imaging such as CT or MRI. Nuclear medicine imaging studies are generally more organ or tissue specific (e.g.: lungs scan, heart scan, bone scan, brain scan, etc.) than those in conventional radiology imaging, which focus on a particular section of the body (e.g.: chest X-ray,



Normal whole body PET/CT scan with FDG-18. The whole body PET/CT scan is commonly used in the detection, staging and follow-up of various cancers.



A nuclear medicine whole body bone scan. The nuclear medicine whole body bone scan is generally used in evaluations of various bone related pathology, such as for bone pain, stress fracture, nonmalignant bone lesions, bone infections, or the spread of cancer to the bone.

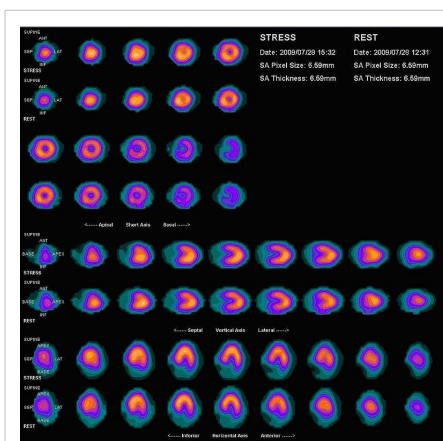
abdomen/pelvis CT scan, head CT scan, etc.). In addition, there are nuclear medicine studies that allow imaging of the whole body based on certain cellular receptors or functions. Examples are whole body PET scan or PET/CT scans, gallium scans, indium white blood cell scans, MIBG and octreotide scans.

While the ability of nuclear metabolism to image disease processes from differences in metabolism is unsurpassed, it is not unique. Certain techniques such as fMRI image tissues (particularly cerebral tissues) by blood flow, and thus show metabolism. Also, contrast-enhancement techniques in both CT and MRI show regions of tissue which are handling pharmaceuticals differently, due to an inflammatory process.

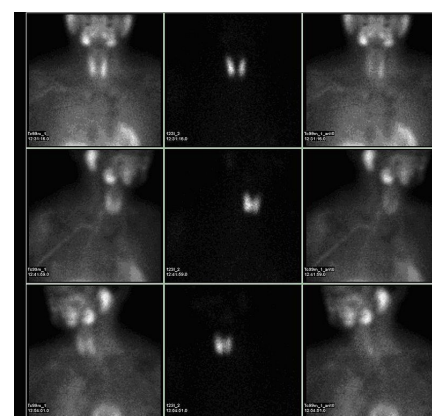
Diagnostic tests in nuclear medicine exploit the way that the body handles substances differently when there is disease or pathology present. The radionuclide introduced into the body is often chemically bound to a complex that acts characteristically within the body; this is commonly known as a tracer. In the presence of disease, a tracer will often be distributed around the body and/or processed differently. For example, the ligand methylene-diphosphonate (MDP) can be preferentially taken up by bone. By chemically attaching technetium-99m to MDP, radioactivity can be transported and attached to bone via the hydroxyapatite for imaging. Any increased physiological function, such as due to a fracture in the bone, will usually mean increased concentration of the tracer. This often results in the appearance of a 'hot-spot' which is a focal increase in radio-accumulation, or a general increase in radio-accumulation throughout the physiological system. Some disease processes result in the exclusion of a tracer, resulting in the appearance of a 'cold-spot'. Many tracer complexes have been developed to image or treat many different organs, glands, and physiological processes.

Hybrid scanning techniques

In some centers, the nuclear medicine scans can be superimposed, using software or hybrid cameras, on images from modalities such as CT or MRI to highlight the part of the body in which the radiopharmaceutical is concentrated. This practice is often referred to as image fusion or co-registration, for example SPECT/CT and PET/CT. The fusion imaging technique in nuclear medicine provides information about the anatomy and function, which would otherwise be unavailable, or would require a more invasive procedure or surgery.



Nuclear Medicine myocardial perfusion scan with Thallium-201 for the rest images (bottom rows) and Tc-Sestamibi for the stress images (top rows). The nuclear medicine myocardial perfusion scan plays a pivotal role in the noninvasive evaluation of coronary artery disease. The study not only identifies patients with coronary artery disease, it also provides overall prognostic information or overall risk of adverse cardiac events for the patient.



A nuclear medicine parathyroid scan demonstrates a parathyroid adenoma adjacent to the left inferior pole of the thyroid gland. . The above study was performed with Technetium-Sestamibi (1st column) and Iodine-123 (2nd column) simultaneous imaging and the subtraction technique (3rd column).

Practical concerns in nuclear imaging

The amount of radiation from diagnostic nuclear medicine procedures is kept within a safe limit and follows the "ALARA" (As Low As Reasonably Achievable) principle. The radiation dose from nuclear medicine imaging varies greatly depending on the type of study. The effective radiation dose can be lower than or compatible to the annual background radiation dose. It can also be in the range or higher than the radiation dose from an abdomen/pelvis CT scan.[2]

Some nuclear medicine procedures require special patient preparation, before the study, to obtain the most accurate result. Pre-imaging preparations may include dietary preparation or withholding of certain medications. Patients are encouraged to consult with the nuclear medicine department prior to a scan.

Nuclear medicine therapy

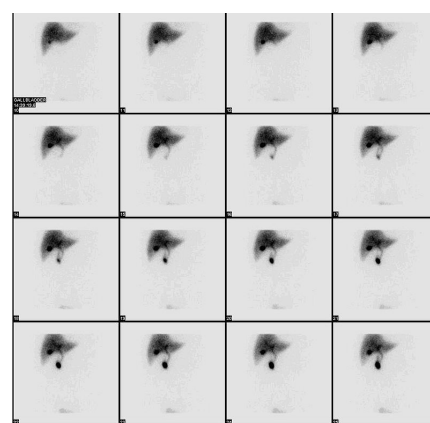
In nuclear medicine therapy, the radiation treatment dose is also administered internally (e.g. intravenous or oral routes) rather from an external radiation source.

The radiopharmaceuticals used in Nuclear Medicine therapy emit ionizing radiation that travels only a short distance, thereby minimizing unwanted side effects and damage to noninvolved organs or nearby structures. Most Nuclear Medicine therapies can be performed as outpatient procedures since there are few side effects from the treatment and the radiation exposure to the general public can be kept within a safe limit. Common Nuclear Medicine therapies include ^{131}I -sodium iodide for hyperthyroidism and thyroid cancer, Yttrium-90-ibritumomab tiuxetan (Zevalin) and Iodine-131-tositumomab (Bexxar) for refractory Lymphoma, ^{131}I -MIBG (metaiodobenzylguanidine) for neuroendocrine tumors, and palliative bone pain treatment with Samarium-153 or Strontium-89. In some centers the nuclear medicine department may also use implanted capsules of isotopes (brachytherapy) to treat cancer.

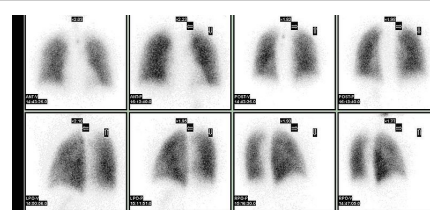
Most nuclear medicine therapies will also require appropriate patient preparation prior to a treatment. Therefore, consultation with the Nuclear Medicine department is recommended prior to therapy.

Molecular medicine

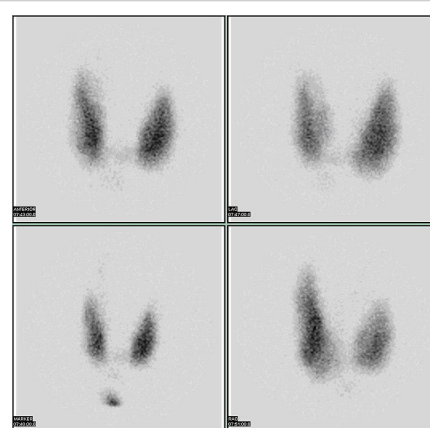
In the future, nuclear medicine may be known as molecular medicine. As our understanding of biological processes in the cells of living organism expands, specific probes can be developed to allow visualization, characterization, and quantification of biologic processes at the cellular and subcellular levels.[2] Nuclear Medicine is an ideal



Normal hepatobiliary scan (HIDA scan). The nuclear medicine hepatobiliary scan is clinically useful in the detection of the gallbladder disease.



Normal pulmonary ventilation and perfusion (V/Q) scan. The nuclear medicine V/Q scan is useful in the evaluation of pulmonary embolism.



Thyroid scan with Iodine-123 for evaluation of hyperthyroidism.

specialty to adapt to the new discipline of molecular medicine, because of its emphasis on function and its utilization of imaging agents that are specific for a particular disease process.

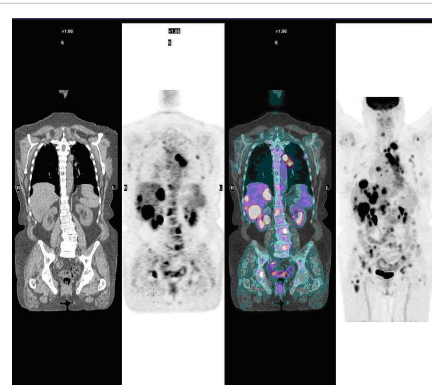
History

The history of nuclear medicine is rich with contributions from gifted scientists across different disciplines in physics, chemistry, engineering, and medicine. The multidisciplinary nature of Nuclear Medicine makes it difficult for medical historians to determine the birthdate of Nuclear Medicine. This can probably be best placed between the discovery of artificial radioactivity in 1934 and the production of radionuclides by Oak Ridge National Laboratory for medicine related use, in 1946.^[3]

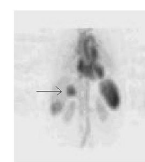
Many historians consider the discovery of artificially produced radioisotopes by Frederic Joliot-Curie and Irene Joliot-Curie in 1934 as the most significant milestone in Nuclear Medicine.^[3] In February 1934, they reported the first artificial production of radioactive material in the *Nature* journal, after discovering radioactivity in aluminum foil that was irradiated with a polonium preparation. Their work built upon earlier discoveries by Wilhelm Konrad Roentgen for X-ray, Henri Becquerel for radioactive uranium salts, and Marie Curie (mother of Irene Curie) for radioactive thorium, polonium and coining the term "radioactivity." Taro Takemi studied the application of nuclear physics to medicine in the 1930s. The history of Nuclear Medicine will not be complete without mentioning these early pioneers.

Nuclear medicine gained public recognition as a potential specialty on December 7, 1946 when an article was published in the *Journal of the American Medical Association* by Sam Seidlin. The article described a successful treatment of a patient with thyroid cancer metastases using radioiodine (I-131). This is considered by many historians as the most important article ever published in Nuclear Medicine.^[4] Although, the earliest use of I-131 was devoted to therapy of thyroid cancer, its use was later expanded to include imaging of the thyroid gland, quantification of the thyroid function, and therapy for hyperthyroidism.

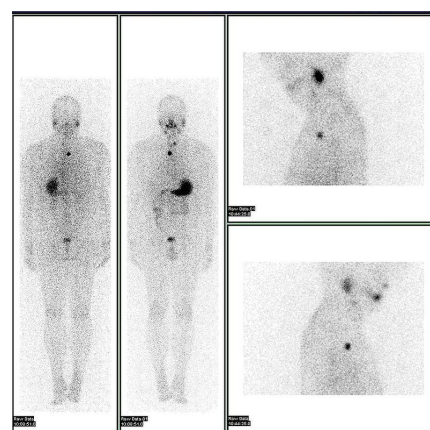
Widespread clinical use of Nuclear Medicine began in the early 1950s, as knowledge expanded about radionuclides, detection of radioactivity, and using certain radionuclides to trace biochemical processes. Pioneering works by Benedict Cassen in developing the first rectilinear scanner and Hal O. Anger's scintillation camera (Anger camera) broadened the young discipline of Nuclear Medicine into a full-fledged medical imaging specialty.



Abnormal whole body PET/CT scan with multiple metastases from a cancer. The whole body PET/CT scan has become an important tool in the evaluation of cancer.



A nuclear medicine SPECT liver scan with technetium-99m labeled autologous red blood cells. A focus of high uptake (arrow) in the liver is consistent with a hemangioma.



Iodine-123 whole body scan for thyroid cancer evaluation. The study above was performed after the total thyroidectomy and TSH stimulation with thyroid hormone medication withdrawal. The study shows a small residual thyroid tissue in the neck and a mediastinum lesion, consistent with the thyroid cancer metastatic disease. The uptakes in the stomach and bowel are normal physiologic findings.

In these years of Nuclear Medicine, the growth was phenomenal. The Society of Nuclear Medicine was formed in 1954 in Spokane, Washington, USA. In 1960, the Society began publication of the Journal of Nuclear Medicine, the premier scientific journal for the discipline in America. There was a flurry of research and development of new radionuclides and radiopharmaceuticals for use with the imaging devices and for in-vitro studies⁵.

Among many radionuclides that were discovered for medical-use, none were as important as the discovery and development of Technetium-99m. It was first discovered in 1937 by C. Perrier and E. Segre as an artificial element to fill space number 43 in the Periodic Table. The development of generator system to produce Technetium-99m in the 1960s became a practical method for medical use. Today, Technetium-99m is the most utilized element in Nuclear Medicine and is employed in a wide variety of Nuclear Medicine imaging studies.

By the 1970s most organs of the body could be visualized using Nuclear Medicine procedures. In 1971, American Medical Association officially recognized nuclear medicine as a medical specialty.^[5] In 1972, the American Board of Nuclear Medicine was established, cementing Nuclear Medicine as a medical specialty.

In the 1980s, radiopharmaceuticals were designed for use in diagnosis of heart disease. The development of single photon emission tomography, around the same time, led to three-dimensional reconstruction of the heart and establishment of the field of Nuclear Cardiology.

More recent developments in Nuclear Medicine include the invention of the first positron emission tomography scanner (PET). The concept of emission and transmission tomography, later developed into single photon emission computed tomography (SPECT), was introduced by David E. Kuhl and Roy Edwards in the late 1950s. Their work led to the design and construction of several tomographic instruments at the University of Pennsylvania. Tomographic imaging techniques were further developed at the Washington University School of Medicine. These innovations led to fusion imaging with SPECT and CT by Bruce Hasegawa from University of California San Francisco (UCSF), and the first PET/CT prototype by D. W. Townsend from University of Pittsburgh in 1998.

PET and PET/CT imaging experienced slower growth in its early years owing to the cost of the modality and the requirement for an on-site or nearby cyclotron. However, an administrative decision to approve medical reimbursement of limited PET and PET/CT applications in oncology has led to phenomenal growth and widespread acceptance over the last few years. PET/CT imaging is now an integral part of oncology for diagnosis, staging and treatment monitoring.

Source of radioisotopes

About two thirds of the world's supply of medical isotopes are produced at the Chalk River Laboratories in Chalk River, Ontario, Canada. The Canadian Nuclear Safety Commission ordered the NRU reactor to be shut down on November 18, 2007 for regularly scheduled maintenance and an upgrade of the safety systems to modern standards. The upgrade took longer than expected and in December 2007 a critical shortage of medical isotopes occurred. The Canadian government unanimously passed emergency legislation, allowing the reactor to re-start on 16 December 2007, and production of medical isotopes to continue.

The Chalk River reactor is used to irradiate materials with neutrons which are produced in great quantity during the fission of U-235. These neutrons change the nucleus of the irradiated material by adding a neutron, or by splitting it in the process of nuclear fission. In a reactor, one of the fission products of uranium is molybdenum-99 which is extracted and shipped to radiopharmaceutical houses all over North America. The Mo-99 radioactively beta decays with a half-life of 2.7 days, turning initially into Tc-99m, which is then extracted (milked) from a "moly cow" (see technetium-99m generator). The Tc-99m then further decays, while inside a patient, releasing a gamma photon which is detected by the gamma camera. It decays to its ground state of Tc-99, which is relatively non-radioactive compared to Tc-99m.

The most commonly used radioisotope in PET F-18, is not produced in any nuclear reactor, but rather in a circular accelerator called a cyclotron. The cyclotron is used to accelerate protons to bombard the stable heavy isotope of

oxygen O-18. The O-18 constitutes about 0.20% of ordinary oxygen (mostly O-16), from which it is extracted. The F-18 is then typically used to make FDG (see this link for more information on this process).

Common isotopes used in nuclear medicine

isotope	symbol	Z	T _{1/2}	decay	photons	β
Imaging:						
fluorine-18	¹⁸ F	9	110 m	β ⁺	511 (193%)	0.664 (97%)
gallium-67	⁶⁷ Ga	31	3.26 d	ec	93 (39%), 185 (21%), 300 (17%)	-
krypton-81m	^{81m} Kr	36	13.1 s	IT	190 (68%)	-
rubidium-82	⁸² Rb	37	1.27 m	β ⁺	511 (191%)	3.379 (95%)
technetium-99m	^{99m} Tc	43	6.01 h	IT	140 (89%)	-
indium-111	¹¹¹ In	49	2.80 d	ec	171 (90%), 245 (94%)	-
iodine-123	¹²³ I	53	13.3 h	ec	159 (83%)	-
xenon-133	¹³³ Xe	54	5.24 d	β ⁻	81 (31%)	0.364 (99%)
thallium-201	²⁰¹ Tl	81	3.04 d	ec	69–83* (94%), 167 (10%)	-
Therapy:						
yttrium-90	⁹⁰ Y	39	2.67 d	β ⁻	-	2.280 (100%)
iodine-131	¹³¹ I	53	8.02 d	β ⁻	364 (81%)	0.807 (100%)
Z = atomic number, the number of protons; T _{1/2} = half-life; decay = mode of decay photons = principle photon energies in kilo-electron volts, keV, (abundance/decay) β = beta maximum energy in mega-electron volts, MeV, (abundance/decay) β ⁺ = β ⁺ decay; β ⁻ = β ⁻ decay; IT = isomeric transition; ec = electron capture * X-rays from progeny, mercury, Hg						

A typical nuclear medicine study involves administration of a radionuclide into the body by intravenous injection in liquid or aggregate form, ingestion while combined with food, inhalation as a gas or aerosol, or rarely, injection of a radionuclide that has undergone micro-encapsulation. Some studies require the labeling of a patient's own blood cells with a radionuclide (leukocyte scintigraphy and red blood cell scintigraphy). Most diagnostic radionuclides emit gamma rays, while the cell-damaging properties of beta particles are used in therapeutic applications. Refined radionuclides for use in nuclear medicine are derived from fission or fusion processes in nuclear reactors, which produce radioisotopes with longer half-lives, or cyclotrons, which produce radioisotopes with shorter half-lives, or take advantage of natural decay processes in dedicated generators, i.e. molybdenum/technetium or strontium/rubidium.

The most commonly used intravenous radionuclides are:

- Technetium-99m (technetium-99m)
- Iodine-123 and 131
- Thallium-201
- Gallium-67

- Fluorine-18 Fluorodeoxyglucose
- Indium-111 Labeled Leukocytes

The most commonly used gaseous/aerosol radionuclides are:

- Xenon-133
- Krypton-81m
- Technetium-99m Technegas^[6]
- Technetium-99m DTPA

Analysis

The end result of the nuclear medicine imaging process is a "dataset" comprising one or more images. In multi-image datasets the array of images may represent a time sequence (i.e. cine or movie) often called a "dynamic" dataset, a cardiac gated time sequence, or a spatial sequence where the gamma-camera is moved relative to the patient. SPECT (single photon emission computed tomography) is the process by which images acquired from a rotating gamma-camera are reconstructed to produce an image of a "slice" through the patient at a particular position. A collection of parallel slices form a slice-stack, a three-dimensional representation of the distribution of radionuclide in the patient.

The nuclear medicine computer may require millions of lines of source code to provide quantitative analysis packages for each of the specific imaging techniques available in nuclear medicine.

Time sequences can be further analysed using kinetic models such as multi-compartment models or a Patlak plot.

Radiation dose

A patient undergoing a nuclear medicine procedure will receive a radiation dose. Under present international guidelines it is assumed that any radiation dose, however small, presents a risk. The radiation doses delivered to a patient in a nuclear medicine investigation present a very small risk of inducing cancer. In this respect it is similar to the risk from X-ray investigations except that the dose is delivered internally rather than from an external source such as an X-ray machine.

The radiation dose from a nuclear medicine investigation is expressed as an effective dose with units of sieverts (usually given in millisieverts, mSv). The effective dose resulting from an investigation is influenced by the amount of radioactivity administered in megabecquerels (MBq), the physical properties of the radiopharmaceutical used, its distribution in the body and its rate of clearance from the body.

Effective doses can range from 6 μ Sv (0.006 mSv) for a 3 MBq chromium-51 EDTA measurement of glomerular filtration rate to 37 mSv for a 150 MBq thallium-201 non-specific tumour imaging procedure. The common bone scan with 600 MBq of technetium-99m-MDP has an effective dose of 3 mSv (1).

Formerly, units of measurement were the curie (Ci), being 3.7×10^{10} Bq, and also 1.0 grams of Radium (Ra-226); the rad (radiation absorbed dose), now replaced by the gray; and the rem (Röntgen equivalent man), now replaced with the sievert. The rad and rem are essentially equivalent for almost all nuclear medicine procedures, and only alpha radiation will produce a higher Rem or Sv value, due to its much higher Relative Biological Effectiveness (RBE). Alpha emitters are nowadays rarely used in nuclear medicine, but were used extensively before the advent of nuclear reactor and accelerator produced radioisotopes. The concepts involved in radiation exposure to humans is covered by the field of Health Physics.

Nuclear Medicine Careers

Nuclear medicine technologist

The information below is adapted from the Society of Nuclear Medicine (SNM) website on Technologist career. For more information and educational requirements, please see training ^[7]

The nuclear medicine technologist works closely with the nuclear medicine physician. Some of the technologist primary responsibilities are to:

- Prepare and administer radioactive chemical compounds, known as radiopharmaceuticals
- Perform patient imaging procedures using sophisticated radiation-detecting instrumentation
- Accomplish computer processing and image enhancement
- Analyze biologic specimens in the laboratory
- Provide images, data analysis, and patient information to the physician for diagnostic interpretation.

During an imaging procedure, the technologist works directly with the patient. The technologist:

- Gains the patient's confidence by obtaining pertinent history, describing the procedure and answering any questions
- Monitors the patient's physical condition during the course of the procedure
- Notes any specific patient's comments which might indicate the need for additional images or might be useful to the physician in interpreting the results of the procedure.

Nuclear medicine technologists work in a wide variety of clinical settings, such as

- Community hospitals
- University-affiliated teaching hospitals and medical centers
- Outpatient imaging facilities
- Public health institutions
- Government and private research institutes.

The physician career in nuclear medicine

Nuclear medicine physicians are primarily responsible for interpretation of diagnostic nuclear medicine scans and treatment of certain diseases, such as cancer, thyroid disease and palliative bone pain.

There are a variety of reasons why physicians have chosen to specialize in nuclear medicine. Some became nuclear medicine physicians because of their interest in nuclear physics and medical imaging. Others may have switched to nuclear medicine after training in other specialties, because of the regular work hours (on average about 8 to 10 hours a day). Others have chosen nuclear medicine because of research opportunities in molecular medicine or molecular imaging.

Nuclear medicine physicians frequently interact with other specialties in medicine and consult on a variety of clinical cases. A nuclear medicine report may save a patient from more invasive or high risk procedures, and/or lead to early disease diagnosis. Nuclear Medicine physicians can be called upon to consult on complex or equivocal clinical cases. Aside from consultations with other physicians, nuclear physicians may directly interact with patients through various nuclear medicine therapies (e.g.: I131 thyroid therapy, refractory lymphoma treatment, palliative bone pain therapy).

A disadvantage of a nuclear medicine career for a physician is that it suffers from low job turnover and a small job market, owing to the specialized nature of the field. Advantages of the field include job satisfaction and more regular hours than many fields of medicine, since very rarely are the procedures in this field performed on an emergency basis.

Nuclear medicine residency/training (physicians)

The information below is adapted from the American Board of Nuclear Medicine (ABNM). For more information, please see ABNM ^[8]

General professional education requirement in the United States of America: graduation from a medical school approved by the Liaison Committee on Medical Education or the American Association of Colleges of Osteopathic Medicine.

In USA the post-doctoral training in nuclear medicine can be approached from three different pathways:

1. If the person has successfully completed an accredited radiology residency then additional ONE year of training in Nuclear Medicine is required to be eligible for ABNM board certification.
2. If the person has successfully completed a clinical residency (e.g. Internal Medicine, Family Medicine, Surgery, Neurology, etc.) then an additional TWO years of training in Nuclear Medicine is required to be eligible for ABNM board certification.
3. If the person has successfully completed one year of preparatory post-doctoral training (internship) then an additional THREE years of training in Nuclear Medicine is required to be eligible for ABNM board certification.

Further reading

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- Taylor A, Schuster DM, Naomi Alazraki N: A Clinicians' Guide to Nuclear Medicine, 2nd edition. Society of Nuclear Medicine, 2000. ISBN 978-0932004727
- Mark J. Shumate MJ, Kooby DA, Alazraki NP: A Clinician's Guide to Nuclear Oncology: Practical Molecular Imaging and Radionuclide Therapies. Society of Nuclear Medicine, January 2007. ISBN 978-0972647885
- Ell P, Gambhir S: Nuclear Medicine in Clinical Diagnosis and Treatment. Churchill Livingstone, 2004. (1950 pages) ISBN 978-0443073120

External links

- Society of Nuclear Medicine ^[9]
- Brochure: What is Nuclear Medicine? ^[10]
- Resource center: information about nuclear medicine ^[11]
- International Atomic Energy Agency (IAEA), Division of Human Health, Nuclear Medicine ^[12]
- RADAR Medical Procedure Radiation Dose Calculator and Consent Language Generator ^[13]

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- [8] Acgme (http://www.acgme.org/acWebsite/navPages/nav_200.asp)
- [9] <http://www.snm.org/>
- [10] <http://interactive.snm.org/docs/whatisnucmed.pdf>
- [11] <http://interactive.snm.org/index.cfm?PageID=6309&RPID=1089>
- [12] <http://www-naweb.iaea.org/nahu/nm/default.asp>
- [13] <http://www.doseinfo-radar.com/RADARDoseRiskCalc.html>

Positron emission tomography

Positron emission tomography (PET) is a nuclear medicine imaging technique which produces a three-dimensional image or picture of functional processes in the body. The system detects pairs of gamma rays emitted indirectly by a positron-emitting radionuclide (tracer), which is introduced into the body on a biologically active molecule. Images of tracer concentration in 3-dimensional or 4-dimensional space (the 4th dimension being time) within the body are then reconstructed by computer analysis. In modern scanners, this reconstruction is often accomplished with the aid of a CT X-ray scan performed on the patient during the same session, in the same machine.

If the biologically active molecule chosen for PET is FDG, an analogue of glucose, the concentrations of tracer imaged then give tissue metabolic activity, in terms of regional glucose uptake. Although use of this tracer results in the most common type of PET scan, other tracer molecules are used in PET to image the tissue concentration of many other types of molecules of interest.



Image of a typical positron emission tomography (PET) facility

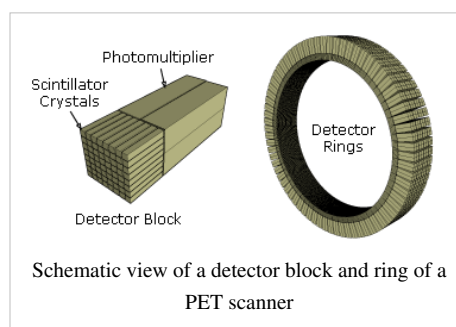


PET/CT-System with 16-slice CT; the ceiling mounted device is an injection pump for CT contrast agent

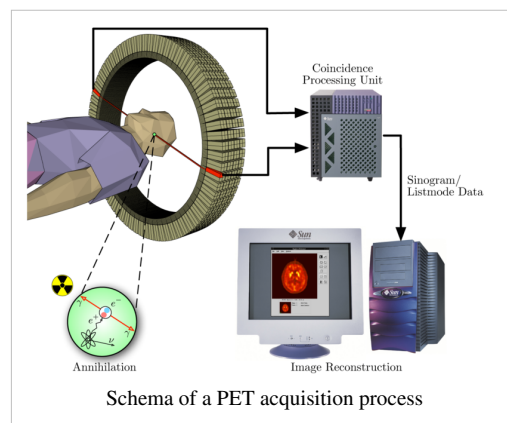
Description

Operation

To conduct the scan, a short-lived radioactive tracer isotope is injected into the living subject (usually into blood circulation). The tracer is chemically incorporated into a biologically active molecule. There is a waiting period while the active molecule becomes concentrated in tissues of interest; then the research subject or patient is placed in the imaging scanner. The molecule most commonly used for this purpose is fluorodeoxyglucose (FDG), a sugar, for which the waiting period is typically an hour. During the scan a record of tissue concentration is made as the tracer decays.



As the radioisotope undergoes positron emission decay (also known as positive beta decay), it emits a positron, an antiparticle of the electron with opposite charge. After travelling up to a few millimeters the positron encounters an electron. The encounter annihilates them both, producing a pair of annihilation (gamma) photons moving in opposite directions. These are detected when they reach a scintillator in the scanning device, creating a burst of light which is detected by photomultiplier tubes or silicon avalanche photodiodes (Si APD). The technique depends on simultaneous or coincident detection of the pair of photons moving in approximately opposite direction (it would be exactly opposite in their center of mass frame, but the scanner has no way to know this, and so has a built-in slight direction-error tolerance). Photons that do not arrive in temporal "pairs" (i.e. within a timing-window of few nanoseconds) are ignored.



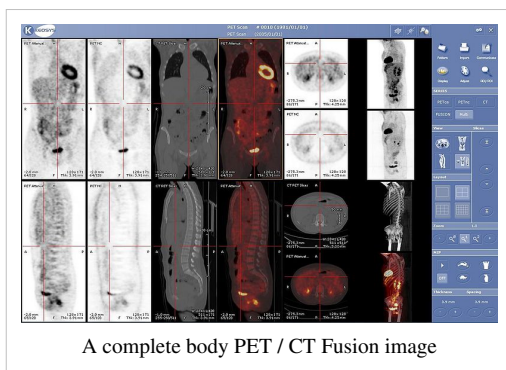
Localization of the positron annihilation event

The most significant fraction of electron-positron decays result in two 511 keV gamma photons being emitted at almost 180 degrees to each other; hence it is possible to localize their source along a straight line of coincidence (also called formally the **line of response** or **LOR**). In practice the LOR has a finite width as the emitted photons are not exactly 180 degrees apart. If the resolving time of the detectors is less than 500 picoseconds rather than about 10 nanoseconds, it is possible to localize the event to a segment of a chord, whose length is determined by the detector timing resolution. As the timing resolution improves, the signal-to-noise ratio (SNR) of the image will improve, requiring fewer events to achieve the same image quality. This technology is not yet common, but it is available on some new systems.^[1]

Image reconstruction using coincidence statistics

More commonly, a technique much like the reconstruction of computed tomography (CT) and single photon emission computed tomography (SPECT) data is used, although the data set collected in PET is much poorer than CT, so reconstruction techniques are more difficult (see Image reconstruction of PET).

Using statistics collected from tens-of-thousands of coincidence events, a set of simultaneous equations for the total activity of each parcel of tissue along many LORs can be solved by a number of techniques, and thus a map of radioactivities as a function of location for parcels or bits of tissue (also called voxels), may be constructed and plotted. The resulting map shows the tissues in which the molecular probe has become concentrated, and can be interpreted by a nuclear medicine physician or radiologist in the context of the patient's diagnosis and treatment plan.



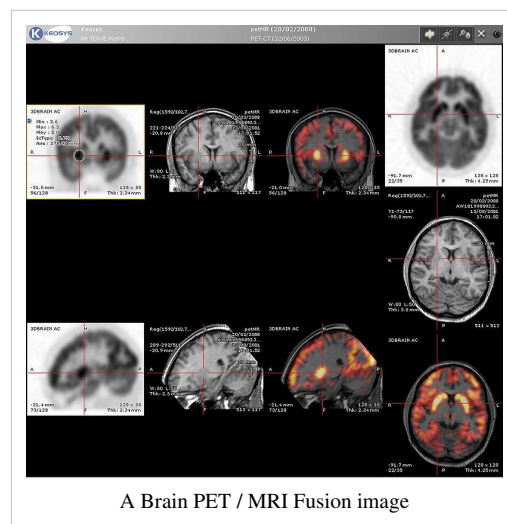
A complete body PET / CT Fusion image

Combination of PET with CT and MRI

PET scans are increasingly read alongside CT or magnetic resonance imaging (MRI) scans, the combination ("co-registration") giving both anatomic and metabolic information (i.e., what the structure is, and what it is doing biochemically). Because PET imaging is most useful in combination with anatomical imaging, such as CT, modern PET scanners are now available with integrated high-end

multi-detector-row CT scanners. Because the two scans can be performed in immediate sequence during the same session, with the patient not changing position between the two types of scans, the two sets of images are more-precisely registered, so that areas of abnormality on the PET imaging can be more perfectly correlated with anatomy on the CT images. This is very useful in showing detailed views of moving organs or structures with higher anatomical variation, which is more common outside the brain.

PET-MRI: At the Jülich Institute of Neurosciences and Biophysics, the world's largest PET/MRI device began operation in April 2009: a 9.4-tesla magnetic resonance tomograph (MRT) combined with a positron emission tomograph (PET). Presently, only the head and brain can be imaged at these high magnetic field strengths.^[2]



A Brain PET / MRI Fusion image

Radionuclides

Radionuclides used in PET scanning are typically isotopes with short half lives such as carbon-11 (~20 min), nitrogen-13 (~10 min), oxygen-15 (~2 min), and fluorine-18 (~110 min). These radionuclides are incorporated either into compounds normally used by the body such as glucose (or glucose analogues), water or ammonia, or into molecules that bind to receptors or other sites of drug action. Such labelled compounds are known as radiotracers. It is important to recognize that PET technology can be used to trace the biologic pathway of any compound in living humans (and many other species as well), provided it can be radiolabeled with a PET isotope. Thus the specific processes that can be probed with PET are virtually limitless, and radiotracers for new target molecules and processes are being synthesized all the time; as of this writing there are already dozens in clinical use and hundreds applied in research. Presently, however, by far the most commonly used nuclide in clinical PET scanning is fluorine-18 in the form of FDG.

Due to the short half lives of most radioisotopes, the radiotracers must be produced using a cyclotron and radiochemistry laboratory that are in close proximity to the PET imaging facility. The half life of fluorine-18 is long enough such that fluorine-18 labeled radiotracers can be manufactured commercially at an offsite location.

Limitations

The minimization of radiation dose to the subject is an attractive feature of the use of short-lived radionuclides. Besides its established role as a diagnostic technique, PET has an expanding role as a method to assess the response to therapy, in particular, cancer therapy,^[3] where the risk to the patient from lack of knowledge about disease progress is much greater than the risk from the test radiation.

Limitations to the widespread use of PET arise from the high costs of cyclotrons needed to produce the short-lived radionuclides for PET scanning and the need for specially adapted on-site chemical synthesis apparatus to produce the radiopharmaceuticals. Few hospitals and universities are capable of maintaining such systems, and most clinical PET is supported by third-party suppliers of radiotracers which can supply many sites simultaneously. This limitation restricts clinical PET primarily to the use of tracers labelled with fluorine-18, which has a half life of 110 minutes and can be transported a reasonable distance before use, or to rubidium-82, which can be created in a portable generator and is used for myocardial perfusion studies. Nevertheless, in recent years a few on-site cyclotrons with integrated shielding and hot labs have begun to accompany PET units to remote hospitals. The presence of the small on-site cyclotron promises to expand in the future as the cyclotrons shrink in response to the high cost of isotope transportation to remote PET machines^[4]

Because the half-life of fluorine-18 is about two hours, the prepared dose of a radiopharmaceutical bearing this radionuclide will undergo multiple half-lives of decay during the working day. This necessitates frequent recalibration of the remaining dose (determination of activity per unit volume) and careful planning with respect to patient scheduling.

Image reconstruction

The raw data collected by a PET scanner are a list of 'coincidence events' representing near-simultaneous detection of annihilation photons by a pair of detectors. Each coincidence event represents a line in space connecting the two detectors along which the positron emission occurred. Modern systems with a high time resolution also use a technique (called "Time-of-flight") where they more precisely decide the difference in time between the detection of the two photons and can thus limit the length of the earlier mentioned line to around 10 cm.

Coincidence events can be grouped into projections images, called sinograms. The sinograms are sorted by the angle of each view and tilt, the latter in 3D case images. The sinogram images are analogous to the projections captured by computed tomography (CT) scanners, and can be reconstructed in a similar way. However, the statistics of the data is much worse than those obtained through transmission tomography. A normal PET data set has millions of counts for the whole acquisition, while the CT can reach a few billion counts. As such, PET data suffer from scatter and random events much more dramatically than CT data does.

In practice, considerable pre-processing of the data is required - correction for random coincidences, estimation and subtraction of scattered photons, detector dead-time correction (after the detection of a photon, the detector must "cool down" again) and detector-sensitivity correction (for both inherent detector sensitivity and changes in sensitivity due to angle of incidence).

Filtered back projection (FBP) has been frequently used to reconstruct images from the projections. This algorithm has the advantage of being simple while having a low requirement for computing resources. However, shot noise in the raw data is prominent in the reconstructed images and areas of high tracer uptake tend to form streaks across the image.

Iterative expectation-maximization algorithms are now the preferred method of reconstruction. The advantage is a better noise profile and resistance to the streak artifacts common with FBP, but the disadvantage is higher computer resource requirements.

Attenuation correction: As different LORs must traverse different thicknesses of tissue, the photons are attenuated differentially. The result is that structures deep in the body are reconstructed as having falsely low tracer uptake. Contemporary scanners can estimate attenuation using integrated x-ray CT equipment, however earlier equipment offered a crude form of CT using a gamma ray (positron emitting) source and the PET detectors.

While attenuation-corrected images are generally more faithful representations, the correction process is itself susceptible to significant artifacts. As a result, both corrected and uncorrected images are always reconstructed and read together.

2D/3D reconstruction: Early PET scanners had only a single ring of detectors, hence the acquisition of data and subsequent reconstruction was restricted to a single transverse plane. More modern scanners now include multiple rings, essentially forming a cylinder of detectors.

There are two approaches to reconstructing data from such a scanner: 1) treat each ring as a separate entity, so that only coincidences within a ring are detected, the image from each ring can then be reconstructed individually (2D reconstruction), or 2) allow coincidences to be detected between rings as well as within rings, then reconstruct the entire volume together (3D).

3D techniques have better sensitivity (because more coincidences are detected and used) and therefore less noise, but are more sensitive to the effects of scatter and random coincidences, as well as requiring correspondingly greater computer resources. The advent of sub-nanosecond timing resolution detectors affords better random coincidence

rejection, thus favoring 3D image reconstruction.

History

The concept of emission and transmission tomography was introduced by David E. Kuhl and Roy Edwards in the late 1950s. Their work later led to the design and construction of several tomographic instruments at the University of Pennsylvania. Tomographic imaging techniques were further developed by Michel Ter-Pogossian, Michael E. Phelps and others at the Washington University School of Medicine.^{[5] [6]}

Work by Gordon Brownell, Charles Burnham and their associates at the Massachusetts General Hospital beginning in the 1950s contributed significantly to the development of PET technology and included the first demonstration of annihilation radiation for medical imaging^[7]. Their innovations, including the use of light pipes, and volumetric analysis have been important in the deployment of PET imaging.

In the 1970s, Tatsuo Ido at the Brookhaven National Laboratory was the first to describe the synthesis of ^{18}F -FDG, the most commonly used PET scanning isotope carrier. The compound was first administered to two normal human volunteers by Abass Alavi in August 1976 at the University of Pennsylvania. Brain images obtained with an ordinary (non-PET) nuclear scanner demonstrated the concentration of FDG in that organ. Later, the substance was used in dedicated positron tomographic scanners, to yield the modern procedure.

The PET/CT scanner, attributed to Dr David Townsend and Dr Nutt was named by TIME Magazine as the medical invention of the year in 2000.

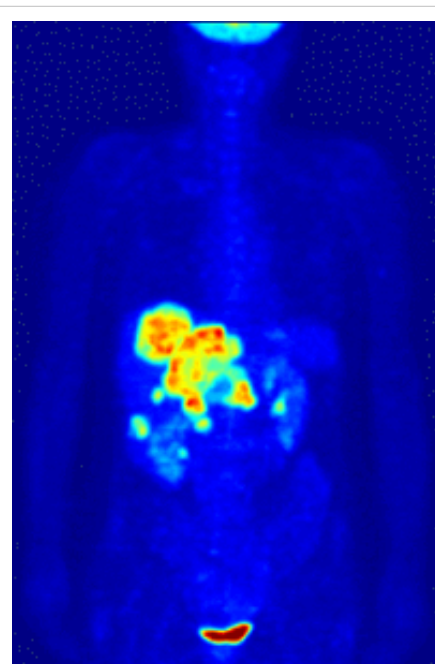
Applications

PET is both a medical and research tool. It is used heavily in clinical oncology (medical imaging of tumors and the search for metastases), and for clinical diagnosis of certain diffuse brain diseases such as those causing various types of dementias. PET is also an important research tool to map normal human brain and heart function.

PET is also used in pre-clinical studies using animals, where it allows repeated investigations into the same subjects. This is particularly valuable in cancer research, as it results in an increase in the statistical quality of the data (subjects can act as their own control) and substantially reduces the numbers of animals required for a given study.

Alternative methods of scanning include x-ray computed tomography (CT), magnetic resonance imaging (MRI) and functional magnetic resonance imaging (fMRI), ultrasound and single photon emission computed tomography (SPECT).

While some imaging scans such as CT and MRI isolate organic anatomic changes in the body, PET and SPECT are capable of detecting areas of molecular biology detail (even prior to anatomic change). PET scanning does this using radiolabelled molecular probes that have different rates of uptake depending on the type and function of tissue involved. Changing of regional blood flow in various anatomic structures (as a measure of the injected positron emitter) can be visualized and relatively quantified with a PET scan.



Maximum intensity projection (MIP) of a F-18 FDG wholebody PET acquisition, showing abnormal focal uptake in the region of the stomach. Normal physiological isotope uptake is seen in the brain, renal collection systems and bladder. In this animation, it is important to view the subject as rotating clockwise (note liver position).

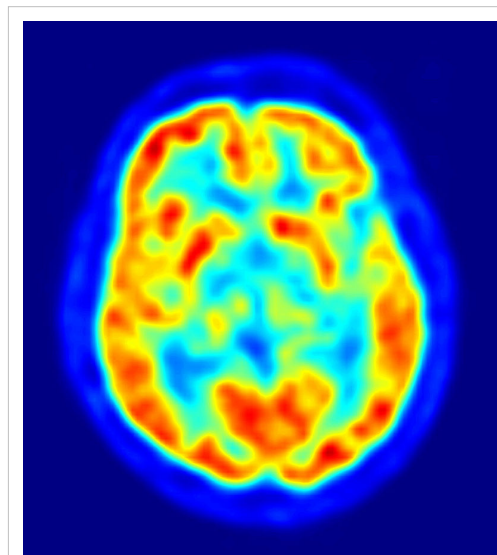
PET imaging is best performed using a dedicated PET scanner. However, it is possible to acquire PET images using a conventional dual-head gamma camera fitted with a coincidence detector. The quality of gamma-camera PET is considerably lower, and acquisition is slower. However, for institutions with low demand for PET, this may allow on-site imaging, instead of referring patients to another center, or relying on a visit by a mobile scanner.

PET is a valuable technique for some diseases and disorders, because it is possible to target the radio-chemicals used for particular bodily functions.

1. **Oncology:** PET scanning with the tracer fluorine-18 (F-18) fluorodeoxyglucose (FDG), called FDG-PET, is widely used in clinical oncology. This tracer is a glucose analog that is taken up by glucose-using cells and phosphorylated by hexokinase (whose mitochondrial form is greatly elevated in rapidly growing malignant tumours). A typical dose of FDG used in an oncological scan is 200-400 MBq for an adult human. Because the oxygen atom which is replaced by F-18 to generate FDG is required for the next step in glucose metabolism in all cells, no further reactions occur in FDG. Furthermore, most tissues (with the notable exception of liver and kidneys) cannot remove the phosphate added by hexokinase. This means that FDG is trapped in any cell which takes it up, until it decays, since phosphorylated sugars, due to their ionic charge, cannot exit from the cell. This results in intense radiolabeling of tissues with high glucose uptake, such as the brain, the liver, and most cancers. As a result, FDG-PET can be used for diagnosis, staging, and monitoring treatment of cancers, particularly in Hodgkin's lymphoma, non-Hodgkin lymphoma, and lung cancer. Many other types of solid tumors will be found to be very highly labeled on a case-by-case basis—a fact which becomes especially useful in searching for tumor metastasis, or for recurrence after a known highly active primary tumor is removed. Because individual PET scans are more expensive than "conventional" imaging with computed tomography (CT) and magnetic resonance imaging (MRI), expansion of FDG-PET in cost-constrained health services will depend on proper health technology assessment; this problem is a difficult one because structural and functional imaging often cannot be directly compared, as they provide different information. Oncology scans using FDG make up over 90% of all PET scans in current practice.

Neurology: PET neuroimaging is based on an assumption that areas of high radioactivity are associated with brain activity. What is actually measured indirectly is the flow of blood to different parts of the brain, which is generally believed to be correlated, and has been measured using the tracer oxygen-15. However, because of its 2-minute half-life O-15 must be piped directly from a medical cyclotron for such uses, and this is difficult. In practice, since the brain is normally a rapid user of glucose, and since brain pathologies such as Alzheimer's disease greatly decrease brain metabolism of both glucose and oxygen in tandem, standard FDG-PET of the brain, which measures regional glucose use, may also be successfully used to differentiate Alzheimer's disease from other dementing processes, and also to make early diagnosis of Alzheimer's disease. The advantage of FDG-PET for these uses is its much wider availability. PET imaging with FDG can also be used for localization of seizure focus: A seizure focus will appear

as hypometabolic during an interictal scan. Several radiotracers (i.e. radioligands) have been developed for PET that are ligands for specific neuroreceptor subtypes such as [^{11}C] raclopride and [^{18}F] fallypride for dopamine D2/D3 receptors, [^{11}C]MeN 5652 and [^{11}C]DASB for serotonin transporters, or enzyme substrates (e.g. 6-FDOPA for the AADC enzyme). These agents permit the visualization of neuroreceptor pools in the context of a plurality of neuropsychiatric and neurologic illnesses. A novel probe developed at the University of Pittsburgh termed PIB



PET scan of the human brain.

(Pittsburgh Compound-B) permits the visualization of amyloid plaques in the brains of Alzheimer's patients. This technology could assist clinicians in making a positive clinical diagnosis of AD pre-mortem and aid in the development of novel anti-amyloid therapies.

3. Cardiology, atherosclerosis and vascular disease study: In clinical cardiology, FDG-PET can identify so-called "hibernating myocardium", but its cost-effectiveness in this role versus SPECT is unclear. Recently, a role has been suggested for FDG-PET imaging of atherosclerosis to detect patients at risk of stroke [8].
4. Neuropsychology / Cognitive neuroscience: To examine links between specific psychological processes or disorders and brain activity.
5. Psychiatry: Numerous compounds that bind selectively to neuroreceptors of interest in biological psychiatry have been radiolabeled with C-11 or F-18. Radioligands that bind to dopamine receptors (D1,D2, reuptake transporter), serotonin receptors (5HT1A, 5HT2A, reuptake transporter) opioid receptors (μ) and other sites have been used successfully in studies with human subjects. Studies have been performed examining the state of these receptors in patients compared to healthy controls in schizophrenia, substance abuse, mood disorders and other psychiatric conditions.
6. Pharmacology: In pre-clinical trials, it is possible to radiolabel a new drug and inject it into animals. Such scans are referred to as biodistribution studies. The uptake of the drug, the tissues in which it concentrates, and its eventual elimination, can be monitored far more quickly and cost effectively than the older technique of killing and dissecting the animals to discover the same information. Much more commonly, however, drug occupancy at a purported site of action can be inferred indirectly by competition studies between unlabeled drug and radiolabeled compounds known apriori to bind with specificity to the site. A single radioligand can be used this way to test many potential drug candidates for the same target. A related technique involves scanning with radioligands that compete with an endogenous (naturally occurring) substance at a given receptor to demonstrate that a drug causes the release of the natural substance.
7. PET technology for small animal imaging: A miniature PET tomograph has been constructed that is small enough for a fully conscious and mobile rat to wear on its head while walking around.^[9] This RatCAP (Rat Conscious Animal PET) allows animals to be scanned without the confounding effects of anesthesia. PET scanners designed specifically for imaging rodents or small primates are marketed for academic and pharmaceutical research.

Pulse Shape Discrimination

The pulse Shape Discrimination (PSD) is a technique used to define which pulse is related to each crystal. Different Techniques were introduced to discriminate between two-types of pulses according to its shape (indeed due to the decay time).

Safety

PET scanning is non-invasive, but it does involve exposure to ionizing radiation. The total dose of radiation is not insignificant, usually around 11 mSv. When compared to the classification level for radiation workers in the UK, of 6 mSv it can be seen that PET scans need proper justification. This can also be compared to 2.2 mSv average annual background radiation in the UK, 0.02 mSv for a chest x-ray and 6.5 - 8 mSv for a CT scan of the chest, according to the Chest Journal and ICRP.^{[10] [11]} A policy change suggested by the IFALPA member associations in year 1999 mentioned that an aircrew member is likely to receive a radiation dose of 4–9 mSv per year.^[12]

See also

- Diffuse optical imaging
- Hot cell (Equipment used to produce the radiopharmaceuticals used in PET)
- Molecular Imaging

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External links

- PET Images ^[13] Search MedPix(r)
- Seeing is believing: In vivo functional real-time imaging of transplanted islets using positron emission tomography (PET)(a protocol) ^[14], Nature Protocols, from Nature Medicine - 12, 1423 - 1428 (2006).
- The nuclear medicine and molecular medicine podcast ^[15] - Podcast
- Positron Emission Particle Tracking ^[16] (PEPT) - engineering analysis tool based on PET that is able to track single particles in 3D within mixing systems or fluidised beds. Developed at the University of Birmingham, UK.
- CMS coverage of PET scans ^[17]

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X-ray computed tomography

Computed tomography (CT) is a medical imaging method employing tomography created by computer processing.^[1] Digital geometry processing is used to generate a three-dimensional image of the inside of an object from a large series of two-dimensional X-ray images taken around a single axis of rotation.^[2]

CT produces a volume of data which can be manipulated, through a process known as "windowing", in order to demonstrate various bodily structures based on their ability to block the X-ray beam. Although historically the images generated were in the axial or transverse plane, orthogonal to the long axis of the body, modern scanners

allow this volume of data to be reformatted in various planes or even as volumetric (3D) representations of structures. Although most common in medicine, CT is also used in other fields, such as nondestructive materials testing. Another example is the DigiMorph project at the University of Texas at Austin which uses a CT scanner to study biological and paleontological specimens.

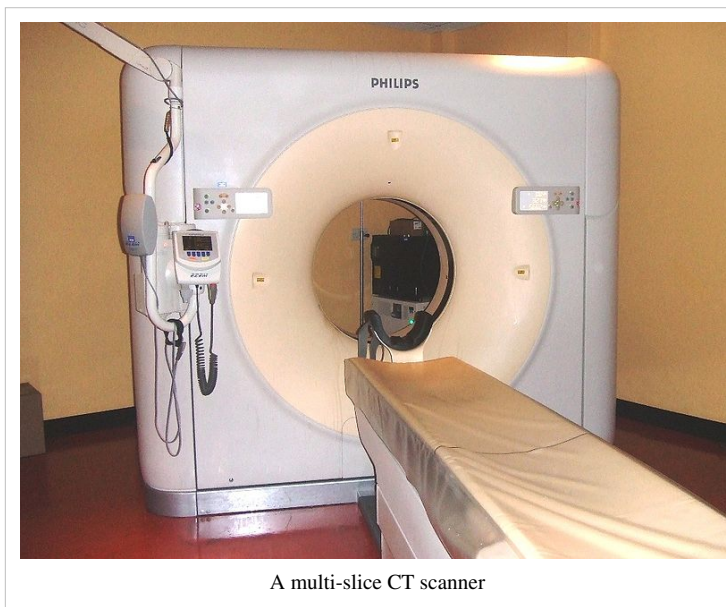
Usage of CT has increased dramatically over the last two decades^[3]. An estimated 72 million scans were performed in the United States in 2007.^[4]

Terminology

The word "tomography" is derived from the Greek *tomos* (slice) and *graphein* (to write). Computed tomography was originally known as the "EMI scan" as it was developed at a research branch of EMI, a company best known today for its music and recording business. It was later known as **computed axial tomography** (CAT or CT scan) and **body section röntgenography**.

Although the term "computed tomography" could be used to describe positron emission tomography and single photon emission computed tomography, in practice it usually refers to the computation of tomography from X-ray images, especially in older medical literature and smaller medical facilities.

In MeSH, "computed axial tomography" was used from 1977–79, but the current indexing explicitly includes "X-ray" in the title.^[5]



A multi-slice CT scanner

History

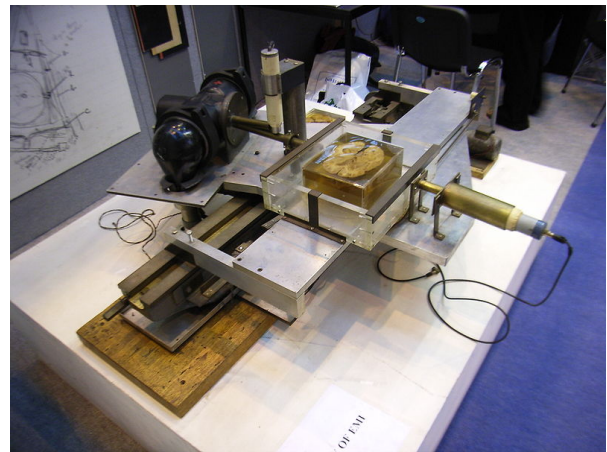
In the early 1900s, the Italian radiologist Alessandro Vallebona proposed a method to represent a single slice of the body on the radiographic film. This method was known as tomography. The idea is based on simple principles of projective geometry: moving synchronously and in opposite directions the X-ray tube and the film, which are connected together by a rod whose pivot point is the focus; the image created by the points on the focal plane appears sharper, while the images of the other points annihilate as noise. This is only marginally effective, as blurring occurs only in the "x" plane. There are also more complex devices which can move in more than one plane and perform more effective blurring.

Tomography had been one of the pillars of radiologic diagnostics until the late 1970s, when the availability of minicomputers and of the transverse axial scanning method, this last due to the work of Godfrey Hounsfield and South African-born Allan McLeod Cormack, gradually supplanted it as the modality of CT.

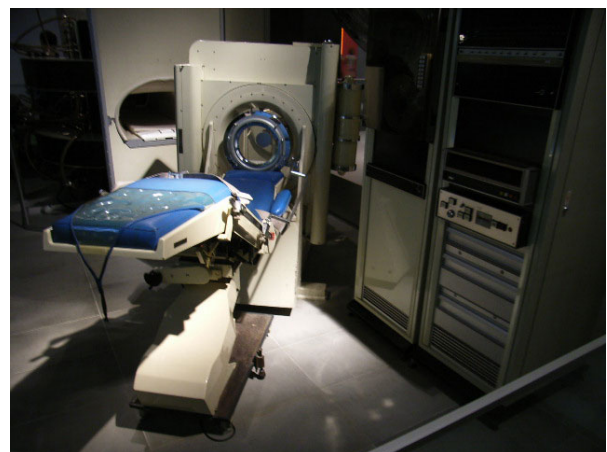
The first commercially viable CT scanner was invented by Sir Godfrey Hounsfield in Hayes, United Kingdom at EMI Central Research Laboratories using X-rays. Hounsfield conceived his idea in 1967,^[6] and it was publicly announced in 1972. Allan McLeod Cormack of Tufts University in Massachusetts independently invented a similar process, and both Hounsfield and Cormack shared the 1979 Nobel Prize in Medicine.^[7]

The original 1971 prototype took 160 parallel readings through 180 angles, each 1° apart, with each scan taking a little over 5 minutes. The images from these scans took 2.5 hours to be processed by algebraic reconstruction techniques on a large computer. The scanner had a single photomultiplier detector, and operated on the Translate/Rotate principle.

It has been claimed that thanks to the success of The Beatles, EMI could fund research and build early models for medical use.^[8] The first production X-ray CT machine (in fact called the "EMI-Scanner") was limited to making tomographic sections of the brain, but acquired the image data in about 4 minutes (scanning two adjacent slices), and the computation time (using a Data General Nova minicomputer) was about 7 minutes per picture. This scanner required the use of a water-filled Perspex tank with a pre-shaped rubber "head-cap" at the front, which enclosed the patient's head. The water-tank was used to reduce the dynamic range of the radiation reaching the detectors (between scanning outside the head compared with scanning through the bone of the skull). The images were relatively low resolution, being composed of a matrix of only 80 x 80 pixels. The first EMI-Scanner was installed in Atkinson Morley Hospital in Wimbledon, England, and the first patient brain-scan was made with it in 1972. In the U.S., the first installation was at the Mayo Clinic. As a tribute to the impact of this system on medical imaging the Mayo Clinic has an EMI scanner on display in the Radiology Department.



The prototype CT scanner



A historic EMI-Scanner

The first CT system that could make images of any part of the body and did not require the "water tank" was the ACTA (Automatic Computerized Transverse Axial) scanner designed by Robert S. Ledley, DDS, at Georgetown University. This machine had 30 photomultiplier tubes as detectors and completed a scan in only 9 translate/rotate cycles, much faster than the EMI-scanner. It used a DEC PDP11/34 minicomputer both to operate the servo-mechanisms and to acquire and process the images. The Pfizer drug company acquired the prototype from the university, along with rights to manufacture it. Pfizer then began making copies of the prototype, calling it the "200FS" (FS meaning Fast Scan), which were selling as fast as they could make them. This unit produced images in a 256×256 matrix, with much better definition than the EMI-Scanner's 80×80.

Previous studies

Tomography

A form of tomography can be performed by moving the X-ray source and detector during an exposure. Anatomy at the target level remains sharp, while structures at different levels are blurred. By varying the extent and path of motion, a variety of effects can be obtained, with variable depth of field and different degrees of blurring of "out of plane" structures.^{[9] :25}

Although largely obsolete, conventional tomography is still used in specific situations such as dental imaging (orthopantomography) or in intravenous urography.

Tomosynthesis

Digital tomosynthesis combines digital image capture and processing with simple tube/detector motion as used in conventional radiographic tomography. Although there are some similarities to CT, it is a separate technique. In CT, the source/detector makes a complete 360-degree rotation about the subject obtaining a complete set of data from which images may be reconstructed. In digital tomosynthesis, only a small rotation angle (e.g., 40 degrees) with a small number of discrete exposures (e.g., 10) are used. This incomplete set of data can be digitally processed to yield images similar to conventional tomography with a limited depth of field. However, because the image processing is digital, a series of slices at different depths and with different thicknesses can be reconstructed from the same acquisition, saving both time and radiation exposure.

Because the data acquired is incomplete, tomosynthesis is unable to offer the extremely narrow slice widths that CT offers. However, higher resolution detectors can be used, allowing very-high in-plane resolution, even if the Z-axis resolution is poor. The primary interest in tomosynthesis is in breast imaging, as an extension to mammography, where it may offer better detection rates with little extra increase in radiation exposure.

Reconstruction algorithms for tomosynthesis are significantly different from conventional CT, because the conventional filtered back projection algorithm requires a complete set of data. Iterative algorithms based upon expectation maximization are most commonly used, but are extremely computationally intensive. Some manufacturers have produced practical systems using off-the-shelf GPUs to perform the reconstruction.

Diagnostic use

Since its introduction in the 1970s, CT has become an important tool in medical imaging to supplement X-rays and medical ultrasonography. It has more recently begun to also be used for preventive medicine or screening for disease, for example CT colonography for patients with a high risk of colon cancer. A number of institutions offer full-body scans for the general population. However, this is a controversial practice, given its lack of proven benefit, cost, radiation exposure, and the risk of finding 'incidental' abnormalities that may trigger additional investigations.

Head

CT scanning of the head is typically used to detect:

1. bleeding, brain injury and skull fractures

Chest

CT can be used for detecting both acute and chronic changes in the lung parenchyma, that is, the internals of the lungs. It is particularly relevant here because normal two dimensional x-rays do not show such defects. A variety of different techniques are used depending on the suspected abnormality. For evaluation of chronic interstitial processes (emphysema, fibrosis, and so forth), thin sections with high spatial frequency reconstructions are used—often scans are performed both in inspiration and expiration. This special technique is called High Resolution CT (HRCT). HRCT is normally done with thin section with skipped areas between the thin sections. Therefore it produces a sampling of the lung and not continuous images. Continuous images are provided in a standard CT of the chest.

For detection of airspace disease (such as pneumonia) or cancer, relatively thick sections and general purpose image reconstruction techniques may be adequate. IV contrast may also be used as it clarifies the anatomy and boundaries of the great vessels and improves assessment of the mediastinum and hilar regions for lymphadenopathy; this is particularly important for accurate assessment of cancer.

CT angiography of the chest is also becoming the primary method for detecting pulmonary embolism (PE) and aortic dissection, and requires accurately timed rapid injections of contrast (Bolus Tracking) and high-speed helical scanners. CT is the standard method of evaluating abnormalities seen on chest X-ray and of following findings of uncertain acute significance. Cardiac CTA is now being used to diagnose coronary artery disease.

According to the 2007 *New England Journal of Medicine* study, 19.2 million (31%) of the 62 million CTs done every year are for lung CTs.

Pulmonary angiogram

CT pulmonary angiogram (CTPA) is a medical diagnostic test used to diagnose pulmonary embolism (PE). It employs computed tomography to obtain an image of the pulmonary arteries.

It is a preferred choice of imaging in the diagnosis of PE due to its minimally invasive nature for the patient, whose only requirement for the scan is a cannula (usually a 20G).

MDCT (multi detector CT) scanners give the optimum resolution and image quality for this test. Images are usually taken on a 0.625 mm slice thickness, although 2 mm is sufficient. 50–100 mls of contrast is given to the patient at a rate of 4 ml/s. The tracker/locator is placed at the level of the pulmonary arteries, which sit roughly at the level of the carina. Images are acquired with the maximum intensity of radio-opaque contrast in the pulmonary arteries. This is done using bolus tracking.

CT machines are now so sophisticated that the test can be done with a patient visit of 5 minutes with an approximate scan time of only 5 seconds or less.

A normal CTPA scan will show the contrast filling the pulmonary vessels, looking bright white. Ideally the aorta should be empty of contrast, to reduce any partial volume artifact which may result in a false positive. Any mass filling defects, such as an embolus, will appear dark in place of the contrast, filling / blocking the space where blood should be flowing into the lungs.

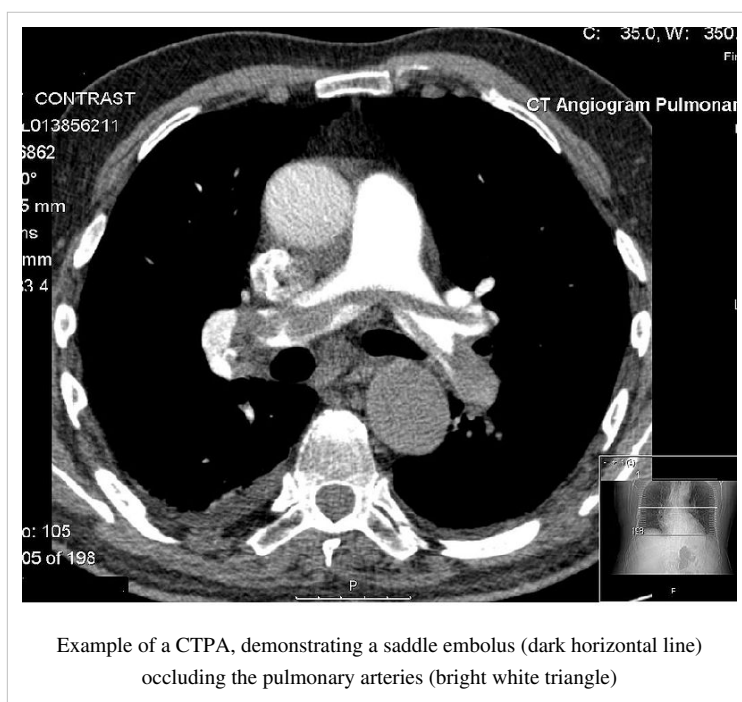
Cardiac

With the advent of subsecond rotation combined with multi-slice CT (up to 64-slice), high resolution and high speed can be obtained at the same time, allowing excellent imaging of the coronary arteries (cardiac CT angiography). Images with an even higher temporal resolution can be formed using retrospective ECG gating. In this technique, each portion of the heart is imaged more than once while an ECG trace is recorded. The ECG is then used to correlate the CT data with their corresponding phases of cardiac contraction. Once this correlation is complete, all data that were recorded while the heart was in motion (systole) can be ignored and images can be made from the remaining data that happened to be acquired while the heart was at rest (diastole). In this way, individual frames in a cardiac CT investigation have a better temporal resolution than the shortest tube rotation time.

Because the heart is effectively imaged more than once (as described above), cardiac CT angiography results in a relatively high radiation exposure around 12 mSv. For the sake of comparison, a chest X-ray carries a dose of approximately $0.02^{[10]}$ to 0.2 mSv and natural background radiation exposure is around 0.01 mSv/day. Thus, cardiac CTA is equivalent to approximately 100-600 chest X-rays or over 3 years worth of natural background radiation. Methods are available to decrease this exposure, however, such as prospectively decreasing radiation output based on the concurrently acquired ECG (aka tube current modulation.) This can result in a significant decrease in radiation exposure, at the risk of compromising image quality if there is any arrhythmia during the acquisition. The significance of radiation doses in the diagnostic imaging range has not been proven, although the possibility of inducing an increased cancer risk across a population is a source of significant concern. This potential risk must be weighed against the competing risk of not performing a test and potentially not diagnosing a significant health problem such as coronary artery disease.

It is uncertain whether this modality will replace invasive coronary catheterization. Currently, it appears that the greatest utility of cardiac CT lies in ruling out coronary artery disease rather than ruling it in. This is because the test has a high sensitivity (greater than 90%) and thus a negative test result means that a patient is very unlikely to have coronary artery disease and can be worked up for other causes of their chest symptoms. This is termed a high negative predictive value. A positive result is less conclusive and often will be confirmed (and possibly treated) with subsequent invasive angiography. The positive predictive value of cardiac CTA is estimated at approximately 82% and the negative predictive value is around 93%.

Dual Source CT scanners, introduced in 2005, allow higher temporal resolution by acquiring a full CT slice in only half a rotation, thus reducing motion blurring at high heart rates and potentially allowing for shorter breath-hold time. This is particularly useful for ill patients who have difficulty holding their breath or who are unable to take heart-rate lowering medication.



The speed advantages of 64-slice MSCT have rapidly established it as the minimum standard for newly installed CT scanners intended for cardiac scanning. Manufacturers are now actively developing 256-slice and true 'volumetric' scanners, primarily for their improved cardiac scanning performance.

The latest MSCT scanners acquire images only at 70-80% of the R-R interval (late diastole). This prospective gating can reduce effective dose from 10-15mSv to as little as 1.2mSv in follow-up patients acquiring at 75% of the R-R interval. Effective doses at a centre with well trained staff doing coronary imaging can average less than the doses for conventional coronary angiography.

Abdominal and pelvic

CT is a sensitive method for diagnosis of abdominal diseases. It is used frequently to determine stage of cancer and to follow progress. It is also a useful test to investigate acute abdominal pain (especially of the lower quadrants, whereas ultrasound is the preferred first line investigation for right upper quadrant pain). Renal stones, appendicitis, pancreatitis, diverticulitis, abdominal aortic aneurysm, and bowel obstruction are conditions that are readily diagnosed and assessed with CT. CT is also the first line for detecting solid organ injury after trauma.

Oral and/or rectal contrast may be used depending on the indications for the scan. A dilute (2% w/v) suspension of barium sulfate is most commonly used. The concentrated barium sulfate preparations used for fluoroscopy e.g. barium enema are too dense and cause severe artifacts on CT. Iodinated contrast agents may be used if barium is contraindicated (for example, suspicion of bowel injury). Other agents may be required to optimize the imaging of specific organs, such as rectally administered gas (air or carbon dioxide) or fluid (water) for a colon study, or oral water for a stomach study.

CT has limited application in the evaluation of the *pelvis*. For the female pelvis in particular, ultrasound and MRI are the imaging modalities of choice. Nevertheless, it may be part of abdominal scanning (e.g. for tumors), and has uses in assessing fractures.

CT is also used in osteoporosis studies and research alongside dual energy X-ray absorptiometry (DXA). Both CT and DXA can be used to assess bone mineral density (BMD) which is used to indicate bone strength, however CT results do not correlate exactly with DXA (the gold standard of BMD measurement). CT is far more expensive, and subjects patients to much higher levels of ionizing radiation, so it is used infrequently.

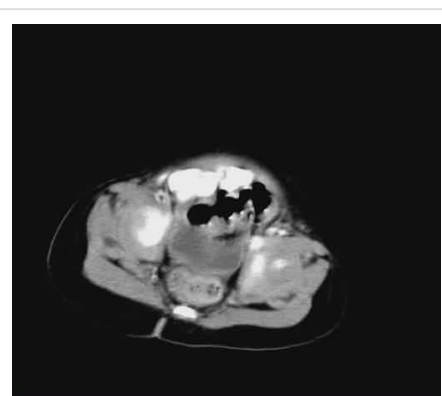
Extremities

CT is often used to image complex fractures, especially ones around joints, because of its ability to reconstruct the area of interest in multiple planes. Fractures, ligamentous injuries and dislocations can easily be recognised with a 0.2 mm resolution.

Advantages and hazards

Advantages over traditional radiography

There are several advantages that CT has over traditional 2D medical radiography. First, CT completely eliminates the superimposition of images of structures outside the area of interest. Second, because of the inherent high-contrast resolution of CT, differences between tissues that differ in physical density by less than 1% can be distinguished. Finally, data from a single CT imaging procedure consisting of either multiple contiguous or one helical scan can be



CT Scan of 11 cm **Wilms' tumor** of right kidney in 13 month old patient.

viewed as images in the axial, coronal, or sagittal planes, depending on the diagnostic task. This is referred to as multiplanar reformatted imaging.

CT is regarded as a moderate to high radiation diagnostic technique. While technical advances have improved radiation efficiency, there has been simultaneous pressure to obtain higher-resolution imaging and use more complex scan techniques, both of which require higher doses of radiation. The improved resolution of CT has permitted the development of new investigations, which may have advantages; compared to conventional angiography for example, CT angiography avoids the invasive insertion of an arterial catheter and guidewire; CT colonography (also known as virtual colonoscopy or VC for short) may be as useful as a barium enema for detection of tumors, but may use a lower radiation dose. CT VC is increasingly being used in the UK as a diagnostic test for bowel cancer and can negate the need for a colonoscopy.

The greatly increased availability of CT, together with its value for an increasing number of conditions, has been responsible for a large rise in popularity. So large has been this rise that, in the most recent comprehensive survey in the United Kingdom, CT scans constituted 7% of all radiologic examinations, but contributed 47% of the total collective dose from medical X-ray examinations in 2000/2001.^[11] Increased CT usage has led to an overall rise in the total amount of medical radiation used, despite reductions in other areas. In the United States and Japan for example, there were 26 and 64 CT scanners per 1 million population in 1996. In the U.S., there were about 3 million CT scans performed in 1980, compared to an estimated 62 million scans in 2006.^[12]

The radiation dose for a particular study depends on multiple factors: volume scanned, patient build, number and type of scan sequences, and desired resolution and image quality. Additionally, two helical CT scanning parameters that can be adjusted easily and that have a profound effect on radiation dose are tube current and pitch.^[13]

Computed tomography (CT) scan has been shown to be more accurate than radiographs in evaluating anterior interbody fusion but may still over-read the extent of fusion.^[14]

Safety concerns

The increased use of CT scans has been the greatest in two fields: screening of adults (screening CT of the lung in smokers, virtual colonoscopy, CT cardiac screening and whole-body CT in asymptomatic patients) and CT imaging of children. Shortening of the scanning time to around 1 second, eliminating the strict need for subject to remain still or be sedated, is one of the main reasons for large increase in the pediatric population (especially for the diagnosis of appendicitis).^[12] CT scans of children have been estimated to produce non-negligible increases in the probability of lifetime cancer mortality, leading to calls for the use of reduced current settings for CT scans of children.^[15] These calculations are based on the assumption of a linear relationship between radiation dose and cancer risk; this claim is controversial, as some but not all evidence shows that smaller radiation doses are less harmful.^[12] Estimated lifetime cancer mortality risks attributable to the radiation exposure from a CT in a 1-year-old are 0.18% (abdominal) and 0.07% (head)—an order of magnitude higher than for adults—although those figures still represent a small increase in cancer mortality over the background rate. In the United States, of approximately 600,000 abdominal and head CT examinations annually performed in children under the age of 15 years, a rough estimate is that 500 of these individuals might ultimately die from cancer attributable to the CT radiation.^[16] The additional risk is still very low (0.35%) compared to the background risk of dying from cancer (23%).^[16] However, if these statistics are extrapolated to the current number of CT scans, the additional rise in cancer mortality could be 1.5 to 2%. Furthermore, certain conditions can require children to be exposed to multiple CT scans. Again, these calculations can be problematic because the assumptions underlying them could overestimate the risk.^[12]

In 2009 a number of studies appeared that further defined the risk of cancer that may be caused by CT scans.^[17] One study indicated that radiation by CT scans is often higher and more variable than cited and each of the 19,500 CT scans that are daily performed in the US is equivalent to 30 to 442 chest x-rays in radiation. It has been estimated that CT radiation exposure will result in 29,000 new cancer cases just from the CT scans performed in 2007.^[17] The most common cancers caused by CT are thought to be lung cancer, colon cancer and leukemia with younger people

and women more at risk. These conclusions, however, are criticized by the American College of Radiology (ACR) that maintains that the life expectancy of CT scanned patients is not that of the general population and that the model of calculating cancer is based on total body radiation exposure and thus faulty.^[17]

CT scans can be performed with different settings for lower exposure in children, although these techniques are often not employed. Surveys have suggested that currently, many CT scans are performed unnecessarily. Ultrasound scanning or magnetic resonance imaging are alternatives (for example, in appendicitis or brain imaging) without the risk of radiation exposure. Although CT scans come with an additional risk of cancer (it can be estimated that the radiation exposure from a full body scan is the same as standing 2.4 km away from the WWII atomic bomb blasts in Japan^[18]), especially in children, the benefits that stem from their use outweighs the risk in many cases.^[16] Studies support informing parents of the risks of pediatric CT scanning.^[19]

Typical scan doses

Examination	Typical effective dose (mSv)	(millirem)
Chest X-ray	0.1	10
Head CT	1.5 ^[20]	150
Screening mammography	3 ^[12]	300
Abdomen CT	5.3 ^[20]	530
Chest CT	5.8 ^[20]	580
CT colonography (virtual colonoscopy)	3.6–8.8	360–880
Chest, abdomen and pelvis CT	9.9 ^[20]	990
Cardiac CT angiogram	6.7–13 ^[21]	670–1300
Barium enema	15 ^[12]	1500
Neonatal abdominal CT	20 ^[12]	2000

For purposes of comparison, the average background exposure in the UK is 1–3 mSv per year.

Adverse reactions to contrast agents

Because contrast CT scans rely on intravenously administered contrast agents in order to provide superior image quality, there is a low but non-negligible level of risk associated with the contrast agents themselves. Many patients report nausea and discomfort, including warmth in the crotch which mimics the sensation of wetting oneself. Certain patients may experience severe and potentially life-threatening allergic reactions to the contrast dye.

The contrast agent may also induce kidney damage. The risk of this is increased with patients who have preexisting renal insufficiency, preexisting diabetes, or reduced intravascular volume. In general, if a patient has normal kidney function, then the risks of contrast nephropathy are negligible. Patients with mild kidney impairment are usually advised to ensure full hydration for several hours before and after the injection. For moderate kidney failure, the use of iodinated contrast should be avoided; this may mean using an alternative technique instead of CT, e.g., MRI. Perhaps paradoxically, patients with severe renal failure requiring dialysis do not require special precautions, as their kidneys have so little function remaining that any further damage would not be noticeable and the dialysis will remove the contrast agent.

Low-dose CT scan

The main issue within radiology today is how to reduce the radiation dose during CT examinations without compromising the image quality. Generally, a high radiation dose results in high-resolution images, while a lower dose leads to increased image noise and results in unsharp images. Unfortunately, as the radiation dose increases, so does the associated risk of radiation induced cancer—a four phase CT abdomen gives the same radiation dose as 300 chest x-rays. However, there are several methods that can be used in order to lower the exposure to ionizing radiation during a CT scan.

1. New software technology can significantly reduce the radiation dose. The software works as a filter that reduces random noise and enhances structures. In this way, it is possible to get high-quality images and at the same time lower the dose by as much as 30 to 70 percent.
2. Individualize the examination and adjust the radiation dose to the body type and body organ examined. Different body types and organs require different amounts of radiation.
3. Prior to every CT examination, evaluate the appropriateness of the exam whether it is motivated or if another type of examination is more suitable. Higher resolution is not always suitable for any given scenario, such as detection of small pulmonary masses^[22]

Computed tomography versus MRI

See the entries on paragraphs of the same name in the MRI and 2D-FT NMRI and Spectroscopy articles. The basic mathematics of the 2D-Fourier transform in CT reconstruction is very similar to the 2D-FT NMRI, but the computer data processing in CT does differ in detail, as for example in the case of the volume rendering or the artifacts elimination algorithms that are specific to CT.

- guidelines for appropriate use of CT, some discussion of MR and Ultrasound as alternatives^[23]

Process

X-ray slice data is generated using an X-ray source that rotates around the object; X-ray sensors are positioned on the opposite side of the circle from the X-ray source. The earliest sensors were scintillation detectors, with photomultiplier tubes excited by (typically) cesium iodide crystals. Cesium iodide was replaced during the 1980s by ion chambers containing high pressure Xenon gas. These systems were in turn replaced by scintillation systems based on photo diodes instead of photomultipliers and modern scintillation materials with more desirable characteristics. Many data scans are progressively taken as the object is gradually passed through the gantry. They are combined together by the mathematical procedures known as tomographic reconstruction. The data are arranged in a matrix in memory, and each data point is convolved with its neighbours according with a seed algorithm using Fast Fourier Transform techniques. This dramatically increases the resolution of each Voxel (volume element). Then a process known as back projection essentially reverses the acquisition geometry and stores the result in another memory array. This data can then be displayed, photographed, or used as input for further processing, such as multi-planar reconstruction.

Newer machines with faster computer systems and newer software strategies can process not only individual cross sections but continuously changing cross sections as the gantry, with the object to be imaged, is slowly and smoothly slid through the X-ray circle. These are called *helical* or *spiral CT* machines. Their computer systems integrate the data of the moving individual slices to generate three dimensional volumetric information (3D-CT scan), in turn viewable from multiple different perspectives on attached CT workstation monitors. This type of data acquisition requires enormous processing power, as the data are arriving in a continuous stream and must be processed in real-time.

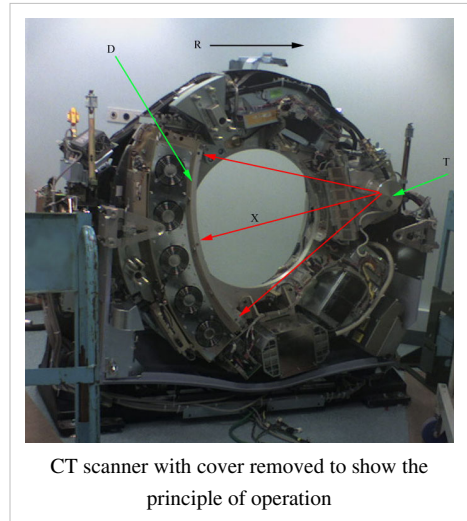
In conventional CT machines, an X-ray tube and detector are physically rotated behind a circular shroud (see the image above right); in the electron beam tomography (EBT) the tube is far larger and higher power to support the

high temporal resolution. The electron beam is deflected in a hollow funnel-shaped vacuum chamber. X-rays are generated when the beam hits the stationary target. The detector is also stationary. This arrangement can result in very fast scans, but is extremely expensive.

The data stream representing the varying radiographic intensity sensed at the detectors on the opposite side of the circle during each sweep is then computer processed to calculate cross-sectional estimations of the radiographic density, expressed in Hounsfield units. Sweeps cover 360 or just over 180 degrees in conventional machines, 220 degrees in EBT.

CT is used in medicine as a diagnostic tool and as a guide for interventional procedures. Sometimes contrast materials such as intravenous iodinated contrast are used. This is useful to highlight structures such as blood vessels that otherwise would be difficult to delineate from their surroundings. Using contrast material can also help to obtain functional information about tissues.

Pixels in an image obtained by CT scanning are displayed in terms of relative radiodensity. The pixel itself is displayed according to the mean attenuation of the tissue(s) that it corresponds to on a scale from +3071 (most attenuating) to -1024 (least attenuating) on the Hounsfield scale. Pixel is a two dimensional unit based on the matrix size and the field of view. When the CT slice thickness is also factored in, the unit is known as a Voxel, which is a three dimensional unit. The phenomenon that one part of the detector cannot differentiate between different tissues is called the "*Partial Volume Effect*". That means that a big amount of cartilage and a thin layer of compact bone can cause the same attenuation in a voxel as hyperdense cartilage alone. Water has an attenuation of 0 Hounsfield units (HU) while air is -1000 HU, cancellous bone is typically +400 HU, cranial bone can reach 2000 HU or more (os temporale) and can cause artifacts. The attenuation of metallic implants depends on atomic number of the element used: Titanium usually has an amount of +1000 HU, iron steel can completely extinguish the X-ray and is therefore responsible for well-known line-artifacts in computed tomograms. Artifacts are caused by abrupt transitions between low- and high-density materials, which results in data values that exceed the dynamic range of the processing electronics.



Artifacts

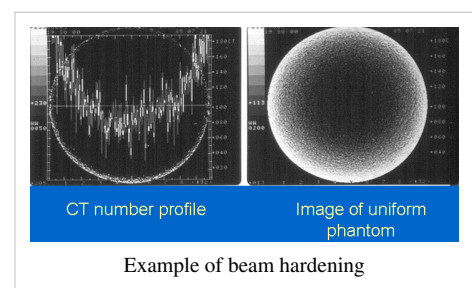
Although CT is a relatively accurate test, it is liable to produce artifacts, such as the following (for more details, see Chapter 3 and 5 of ref.^[21]).

- **Aliasing artifact or streaks**

These appear as dark lines which radiate away from sharp corners. It occurs because it is impossible for the scanner to "sample" or take enough projections of the object, which is usually metallic. It can also occur when an insufficient X-ray tube current is selected, and insufficient penetration of the x-ray occurs. These artifacts are also closely tied to motion during a scan. This type of artifact commonly occurs in head images around the pituitary fossa area.

- **Partial volume effect**

This appears as "blurring" over sharp edges. It is due to the scanner being unable to differentiate between a small amount of high-density material (e.g. bone) and a larger amount of lower density (e.g., cartilage). The processor tries to average out the two densities or structures, and information is lost. This can be partially overcome by scanning



using thinner slices.

- **Ring artifact**

Probably the most common mechanical artifact, the image of one or many "rings" appears within an image. This is usually due to a detector fault.

- **Noise artifact**

This appears as graining on the image and is caused by a low signal to noise ratio. This occurs more commonly when a thin slice thickness is used. It can also occur when the power supplied to the X-ray tube is insufficient to penetrate the anatomy.

- **Motion artifact**

This is seen as blurring and/or streaking which is caused by movement of the object being imaged.

- **Windmill**

Streaking appearances can occur when the detectors intersect the reconstruction plane. This can be reduced with filters or a reduction in pitch.

- **Beam hardening**

This can give a "cupped appearance". It occurs when there is more attenuation in the center of the object than around the edge. This is easily corrected by filtration and software.

Three-dimensional (3D) image reconstruction

The principle

Because contemporary CT scanners offer isotropic or near isotropic, resolution, display of images does not need to be restricted to the conventional axial images. Instead, it is possible for a software program to build a volume by "stacking" the individual slices one on top of the other. The program may then display the volume in an alternative manner.^[24]

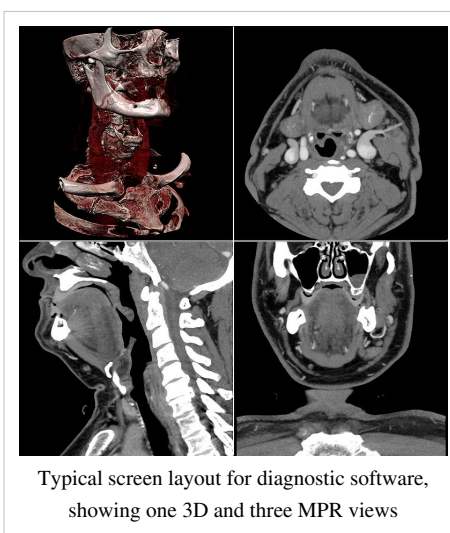
Multiplanar reconstruction

Multiplanar reconstruction (MPR) is the simplest method of reconstruction. A volume is built by stacking the axial slices. The software then cuts slices through the volume in a different plane (usually orthogonal). Optionally, a special projection method, such as maximum-intensity projection (MIP) or minimum-intensity projection (mIP), can be used to build the reconstructed slices.

MPR is frequently used for examining the spine. Axial images through the spine will only show one vertebral body at a time and cannot reliably show the intervertebral discs. By reformatting the volume, it becomes much easier to visualise the position of one vertebral body in relation to the others.

Modern software allows reconstruction in non-orthogonal (oblique) planes so that the optimal plane can be chosen to display an anatomical structure. This may be particularly useful for visualising the structure of the bronchi as these do not lie orthogonal to the direction of the scan.

For vascular imaging, curved-plane reconstruction can be performed. This allows bends in a vessel to be "straightened" so that the entire length can be visualised on one image, or a short series of images. Once a vessel has been "straightened" in this way, quantitative measurements of length and cross sectional area can be made, so that



Typical screen layout for diagnostic software, showing one 3D and three MPR views

surgery or interventional treatment can be planned.

MIP reconstructions enhance areas of high radiodensity, and so are useful for angiographic studies. mIP reconstructions tend to enhance air spaces so are useful for assessing lung structure.

3D rendering techniques

Surface rendering

A threshold value of radiodensity is chosen by the operator (e.g. a level that corresponds to bone). A threshold level is set, using edge detection image processing algorithms. From this, a three-dimensional model can be constructed and displayed on screen. Multiple models can be constructed from various different thresholds, allowing different colors to represent each anatomical component such as bone, muscle, and cartilage. However, the interior structure of each element is not visible in this mode of operation.

Volume rendering

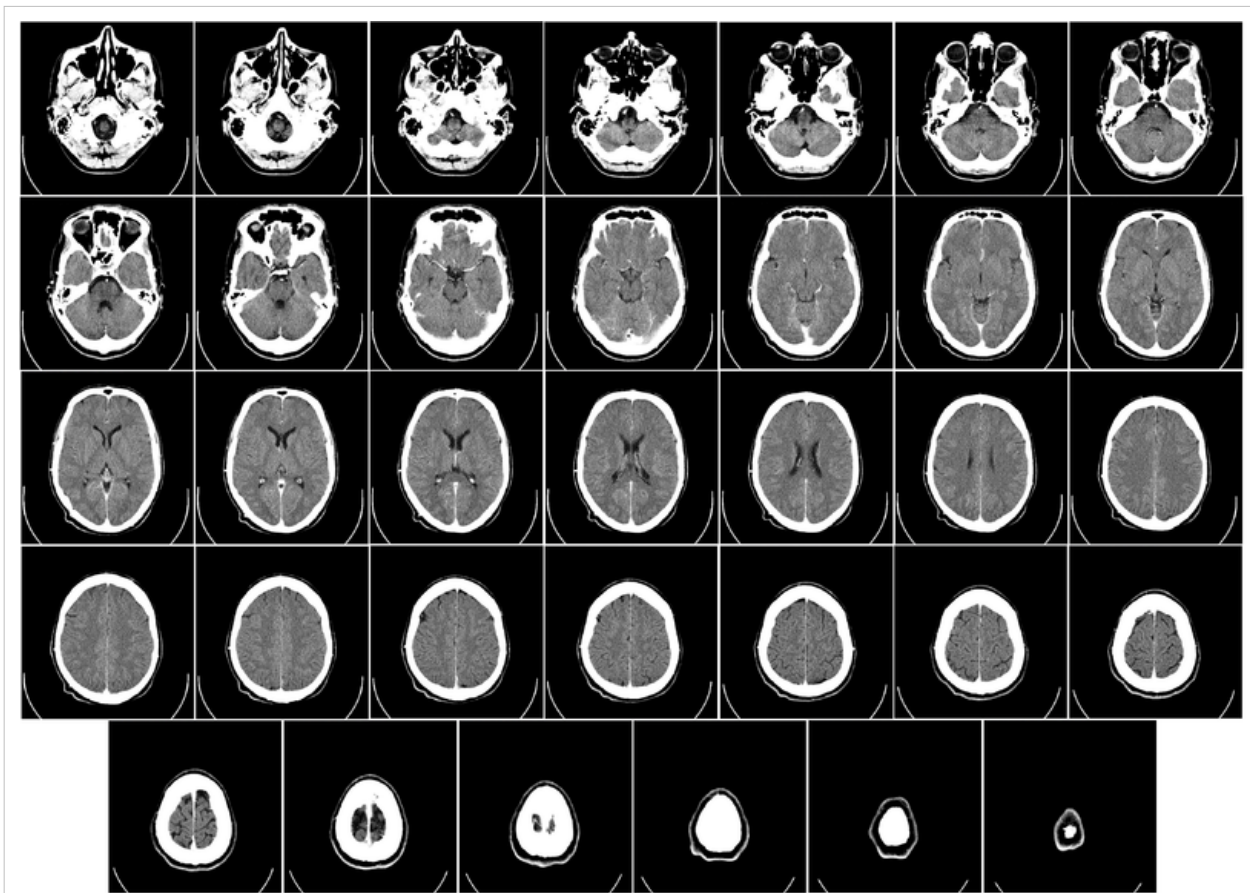
Surface rendering is limited in that it will only display surfaces which meet a threshold density, and will only display the surface that is closest to the imaginary viewer. In volume rendering, transparency and colors are used to allow a better representation of the volume to be shown in a single image—e.g. the bones of the pelvis could be displayed as semi-transparent, so that even at an oblique angle, one part of the image does not conceal another.

Image segmentation

Where different structures have similar radiodensity, it can become impossible to separate them simply by adjusting volume rendering parameters. The solution is called segmentation, a manual or automatic procedure that can remove the unwanted structures from the image.

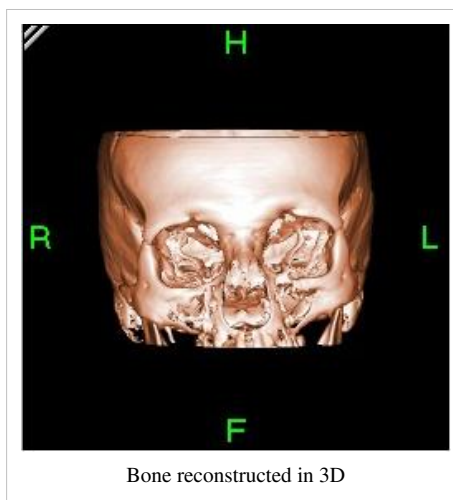
Example

Some slices of a cranial CT scan are shown below. The bones are whiter than the surrounding area. (Whiter means higher attenuation.) Note the blood vessels (arrowed) showing brightly due to the injection of an iodine-based contrast agent.



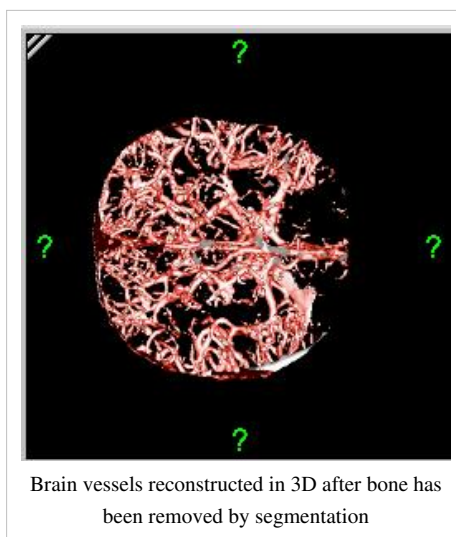
Computed tomography of human brain, from base of the skull to top. Taken with intravenous contrast medium.

A volume rendering of this volume clearly shows the high density bones.



Bone reconstructed in 3D

After using a segmentation tool to remove the bone, the previously concealed vessels can now be demonstrated.



See also

- Virtopsy
- Xenon-enhanced CT scanning

External links

- Open-source computed tomography simulator with educational tracing displays ^[25]
- idoimaging.com: Free software for viewing CT and other medical imaging files ^[26]
- CT Artefacts ^[27] by David Platten
- DigiMorph ^[28] A library of 3D imagery based on CT scans of the internal and external structure of living and extinct plants and animals.
- MicroCT and calcified tissues ^[29] A website dedicated to microCT in the microscopic analysis of calcified tissues.
- Free Radiology Resource for Radiologists, Radiographers, and Technical Assistance ^[30]
- Radiation Risk Calculator ^[31] Calculate cancer risk from CT scans and xrays.
- CT scanner video - gantry ^[32]
- CT in your clinical practice ^[33] by Gregory J. Kohs and Joel Legunn.
- Coronary CT angiography by Eugene Lin ^[34]
- CT physics lecture ^[35] excellent video lectures about physics in computed tomography

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- [29] http://www.med.univ-angers.fr/discipline/lab_histo/page_microCT.htm
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- [31] <http://www.xrayrisk.com>
- [32] <http://www.radrounds.com/video/ct-scanner-gantry-full-speed>
- [33] <http://www.ajronline.org/cgi/data/183/3/DC1/1>
- [34] <http://emedicine.medscape.com/article/1603072-overview>
- [35] http://www.radiopolis.com/index.php/radiology-videos/video-gallery.html?task=viewvideo&video_id=122

Magnetic resonance imaging

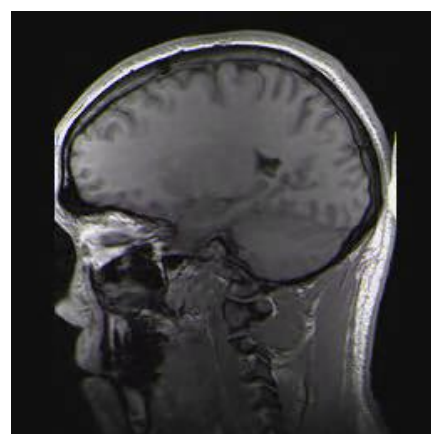
Magnetic resonance imaging (MRI), or **nuclear magnetic resonance imaging (NMRI)**, is primarily a medical imaging technique most commonly used in radiology to visualize detailed internal structure and limited function of the body. MRI provides much greater contrast between the different soft tissues of the body than computed tomography (CT) does, making it especially useful in neurological (brain), musculoskeletal, cardiovascular, and oncological (cancer) imaging. Unlike CT, it uses no ionizing radiation, but uses a powerful magnetic field to align the nuclear magnetization of (usually) hydrogen atoms in water in the body. Radio frequency (RF) fields are used to systematically alter the alignment of this magnetization, causing the hydrogen nuclei to produce a rotating magnetic field detectable by the scanner. This signal can be manipulated by additional magnetic fields to build up enough information to construct an image of the body.^[1] :36

Magnetic resonance imaging is a relatively new technology. The first MR image was published in 1973^[2] ^[3] and the first cross-sectional image of a living mouse was published in January 1974.^[4] The first studies performed on humans were published in 1977.^[5] ^[6] By comparison, the first human X-ray image was taken in 1895.

Magnetic resonance imaging was developed from knowledge gained in the study of nuclear magnetic resonance. In its early years the technique was referred to as nuclear magnetic resonance imaging (NMRI). However, because the word *nuclear* was associated in the public mind with ionizing radiation exposure it is generally now referred to simply as MRI. Scientists still use the term NMRI when discussing non-medical devices operating on the same principles. The term magnetic resonance tomography (MRT) is also sometimes used.



Sagittal MR image of the knee



Para-sagittal MRI of the head, with aliasing artifacts (nose and forehead appear at the back of the head)

How MRI works

The body is largely composed of water molecules which each contain two hydrogen nuclei or protons. When a person goes inside the powerful magnetic field of the scanner, the magnetic moments of some of these protons align with the direction of the field.

A radio frequency transmitter is then briefly turned on, producing an electromagnetic field. In simple terms, the photons of this field have just the right energy, known as the resonance frequency, to flip the spin of the aligned protons. As the intensity and duration of the field increases, more aligned spins are affected. After the field is turned off, the protons decay to the original spin-down state and the difference in energy between the two states is released as a photon. It is these photons that produce the signal which can be detected by the scanner. The frequency at which the protons resonate depends on the strength of the magnetic field. As a result of conservation of energy, this also dictates the frequency of the released photons.

It is this relationship between field-strength and frequency that allows the use of nuclear magnetic resonance for imaging. Additional magnetic fields are applied during the scan in order to make the magnetic field strength depend

on the position within the patient, providing a straightforward method to control where the protons are excited by the radio photons. These fields are created by passing electric currents through solenoids, known as gradient coils. Since these coils are within the bore of the scanner, there will be large forces between them and the main field coils, producing most of the noise that is heard during operation. Without efforts to dampen this noise, it can approach 130 decibels (the human pain threshold) with strong fields^[7].

An image can be constructed because the protons in different tissues return to their equilibrium state at different rates. By changing the parameters on the scanner this effect is used to create contrast between different types of body tissue or between other properties, as in fMRI and diffusion MRI.

Contrast agents may be injected intravenously to enhance the appearance of blood vessels, tumors or inflammation. Contrast agents may also be directly injected into a joint in the case of arthrograms, MRI images of joints. Unlike CT, MRI uses no ionizing radiation and is generally a very safe procedure. Nonetheless the strong magnetic fields and radio pulses can affect metal implants, including cochlear implants and cardiac pacemakers. In the case of cardiac pacemakers, the results can sometimes be lethal^[8], so patients with such implants are generally not eligible for MRI.

MRI is used to image every part of the body, and is particularly useful for tissues with many hydrogen nuclei and little density contrast, such as the brain, muscle, connective tissue and most tumors.

Applications

In clinical practice, MRI is used to distinguish pathologic tissue (such as a brain tumor) from normal tissue. One advantage of an MRI scan is that it is believed to be harmless to the patient. It uses strong magnetic fields and non-ionizing radiation in the radio frequency range, unlike CT scans and traditional X-rays which both use of ionizing radiation.

While CT provides good spatial resolution (the ability to distinguish two structures an arbitrarily small distance from each other as separate), MRI provides comparable resolution with far better contrast resolution (the ability to distinguish the differences between two arbitrarily similar but not identical tissues). The basis of this ability is the complex library of *pulse sequences* that the modern medical MRI scanner includes, each of which is optimized to provide *image contrast* based on the chemical sensitivity of MRI.

For example, with particular values of the *echo time* (T_E) and the *repetition time* (T_R), which are basic parameters of image acquisition, a sequence will take on the property of T_2 -weighting. On a T_2 -weighted scan, water- and fluid-containing tissues are bright (most modern T_2 sequences are actually *fast* T_2 sequences) and fat-containing tissues are dark. The reverse is true for T_1 -weighted images. Damaged tissue tends to develop edema, which makes a T_2 -weighted sequence sensitive for pathology, and generally able to distinguish pathologic tissue from normal tissue. With the addition of an additional radio frequency pulse and additional manipulation of the magnetic gradients, a T_2 -weighted sequence can be converted to a **FLAIR** sequence, in which free water is now dark, but edematous tissues remain bright. This sequence in particular is currently the most sensitive way to evaluate the brain for demyelinating diseases, such as multiple sclerosis.

The typical MRI examination consists of 5–20 sequences, each of which are chosen to provide a particular type of information about the subject tissues. This information is then synthesized by the interpreting physician.

Basic MRI scans

T_1 -weighted MRI

T_1 -weighted scans use a gradient echo (GRE) sequence, with short T_E and short T_R . This is one of the basic types of MR contrast and is a commonly run clinical scan. The T_1 weighting can be increased (improving contrast) with the use of an inversion pulse as in an MP-RAGE sequence. Due to the short repetition time (T_R) this scan can be run very fast allowing the collection of high resolution 3D datasets. A T_1 reducing gadolinium contrast agent is also commonly used, with a T_1 scan being collected before and after administration of contrast agent to compare the difference. In the brain T_1 -weighted scans provide good gray matter/white matter contrast.

T_2 -weighted MRI

T_2 -weighted scans use a spin echo (SE) sequence, with long T_E and long T_R . They have long been the clinical workhorse as the spin echo sequence is less susceptible to inhomogeneities in the magnetic field. They are particularly well suited to edema as they are sensitive to water content (edema is characterized by increased water content).

T_2^* -weighted MRI

T_2^* (pronounced "T 2 star") weighted scans use a gradient echo (GRE) sequence, with long T_E and long T_R . The gradient echo sequence used does not have the extra refocusing pulse used in spin echo so it is subject to additional losses above the normal T_2 decay (referred to as T_2'), these taken together are called T_2^* . This also makes it more prone to susceptibility losses at air/tissue boundaries, but can increase contrast for certain types of tissue, such as venous blood.

Spin density weighted MRI

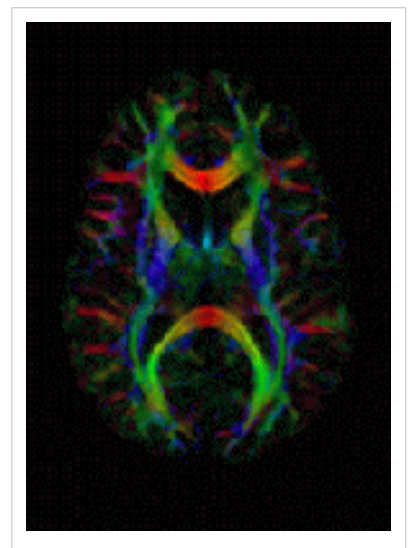
Spin density, also called proton density, weighted scans try to have no contrast from either T_2 or T_1 decay, the only signal change coming from differences in the amount of available spins (hydrogen nuclei in water). It uses a spin echo or sometimes a gradient echo sequence, with short T_E and long T_R .

Specialized MRI scans

Diffusion MRI

Diffusion MRI measures the diffusion of water molecules in biological tissues.^[9] In an isotropic medium (inside a glass of water for example) water molecules naturally move randomly according to Brownian motion. In biological tissues however, the diffusion may be anisotropic. For example a molecule inside the axon of a neuron has a low probability of crossing the myelin membrane. Therefore the molecule will move principally along the axis of the neural fiber. If we know that molecules in a particular voxel diffuse principally in one direction we can make the assumption that the majority of the fibers in this area are going parallel to that direction.

The recent development of diffusion tensor imaging (DTI)^[3] enables diffusion to be measured in multiple directions and the fractional anisotropy in each direction to be calculated for each voxel. This enables researchers to make brain maps of fiber directions to examine the connectivity of different regions in the brain (using tractography) or to examine areas of neural degeneration and demyelination in diseases like Multiple Sclerosis.



Another application of diffusion MRI is diffusion-weighted imaging (DWI). Following an ischemic stroke, DWI is highly sensitive to the changes occurring in the lesion.^[10] It is speculated that increases in restriction (barriers) to water diffusion, as a result of cytotoxic edema (cellular swelling), is responsible for the increase in signal on a DWI scan. The DWI enhancement appears within 5–10 minutes of the onset of stroke symptoms (as compared with computed tomography, which often does not detect changes of acute infarct for up to 4–6 hours) and remains for up to two weeks. Coupled with imaging of cerebral perfusion, researchers can highlight regions of "perfusion/diffusion mismatch" that may indicate regions capable of salvage by reperfusion therapy.

Like many other specialized applications, this technique is usually coupled with a fast image acquisition sequence, such as echo planar imaging sequence.

Magnetization Transfer MRI

Magnetization transfer (MT) refers to the transfer of longitudinal magnetization from free water protons to hydration water protons in NMR and MRI.

In magnetic resonance imaging of molecular solutions, such as protein solutions, two types of water molecules, free (bulk) and hydration, are found. Free water protons have faster average rotational frequency and hence less fixed water molecules that may cause local field inhomogeneity. Because of this uniformity, most free water protons have resonance frequency lying narrowly around the normal proton resonance frequency of 63 MHz (at 1.5 teslas). This also results in slower transverse magnetization dephasing and hence longer T_2 . Conversely, hydration water molecules are slowed down by interaction with solute molecules and hence create field inhomogeneities that lead to wider resonance frequency spectrum.

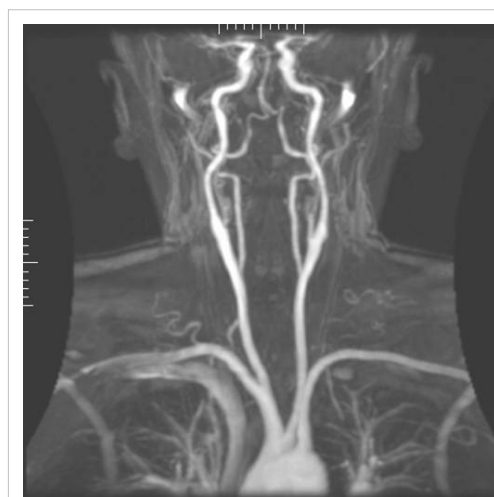
Fluid attenuated inversion recovery (FLAIR)

Fluid Attenuated Inversion Recovery (FLAIR)^[11] is an inversion-recovery pulse sequence used to null signal from fluids. For example, it can be used in brain imaging to suppress cerebrospinal fluid (CSF) so as to bring out the periventricular hyperintense lesions, such as multiple sclerosis (MS) plaques. By carefully choosing the inversion time TI (the time between the inversion and excitation pulses), the signal from any particular tissue can be suppressed.

Magnetic resonance angiography

Magnetic resonance angiography (MRA) is used to generate pictures of the arteries in order to evaluate them for stenosis (abnormal narrowing) or aneurysms (vessel wall dilatations, at risk of rupture). MRA is often used to evaluate the arteries of the neck and brain, the thoracic and abdominal aorta, the renal arteries, and the legs (called a "run-off"). A variety of techniques can be used to generate the pictures, such as administration of a paramagnetic contrast agent (gadolinium) or using a technique known as "flow-related enhancement" (e.g. 2D and 3D time-of-flight sequences), where most of the signal on an image is due to blood which has recently moved into that plane, see also FLASH MRI. Techniques involving phase accumulation (known as phase contrast angiography) can also be used to generate flow velocity maps easily and accurately. Magnetic resonance venography (MRV) is a similar procedure that is used to image veins. In this

method the tissue is now excited inferiorly while signal is gathered in the plane immediately superior to the excitation plane, and thus imaging the venous blood which has recently moved from the excited plane^[12].



Magnetic Resonance Angiography

Magnetic resonance gated intracranial CSF dynamics (MR-GILD)

Magnetic resonance gated intracranial cerebrospinal fluid (CSF) or liquor dynamics (MR-GILD) technique is an MR sequence based on bipolar gradient pulse used to demonstrate CSF pulsatile flow in ventricles, cisterns, aqueduct of Sylvius and entire intracranial CSF pathway. It is a method for analyzing CSF circulatory system dynamics in patients with CSF obstructive lesions such as normal pressure hydrocephalus. It also allows visualization of both arterial and venous pulsatile blood flow in vessels without use of contrast agents.^{[13] [14]}

Diastolic time data acquisition (DTDA).	Systolic time data acquisition (STDA).
	

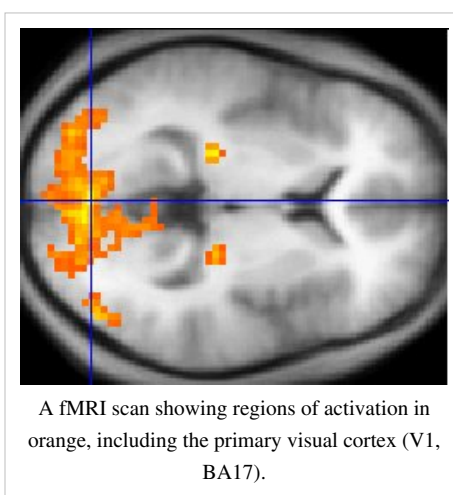
Magnetic resonance spectroscopy

Magnetic resonance spectroscopy (MRS) is used to measure the levels of different metabolites in body tissues. The MR signal produces a spectrum of resonances that correspond to different molecular arrangements of the isotope being "excited". This signature is used to diagnose certain metabolic disorders, especially those affecting the brain,^[15] and to provide information on tumor metabolism.^[16]

Magnetic resonance spectroscopic imaging (MRSI) combines both spectroscopic and imaging methods to produce spatially localized spectra from within the sample or patient. The spatial resolution is much lower (limited by the available SNR), but the spectra in each voxel contains information about many metabolites. Because the available signal is used to encode spatial and spectral information, MRSI requires high SNR achievable only at higher field strengths (3 T and above).

Functional MRI

Functional MRI (fMRI) measures signal changes in the brain that are due to changing neural activity. The brain is scanned at low resolution but at a rapid rate (typically once every 2–3 seconds). Increases in neural activity cause changes in the MR signal via T_2^* changes;^[17] this mechanism is referred to as the BOLD (blood-oxygen-level dependent) effect. Increased neural activity causes an increased demand for oxygen, and the vascular system actually overcompensates for this, increasing the amount of oxygenated hemoglobin relative to deoxygenated hemoglobin. Because deoxygenated hemoglobin attenuates the MR signal, the vascular response leads to a signal increase that is related to the neural activity. The precise nature of the relationship between neural activity and the BOLD signal is a subject of current research. The BOLD effect also allows for the generation of high resolution 3D maps of the venous vasculature within neural tissue.



While BOLD signal is the most common method employed for neuroscience studies in human subjects, the flexible nature of MR imaging provides means to sensitize the signal to other aspects of the blood supply. Alternative techniques employ arterial spin labeling (ASL) or weight the MRI signal by cerebral blood flow (CBF) and cerebral blood volume (CBV). The CBV method requires injection of a class of MRI contrast agents that are now in human

clinical trials. Because this method has been shown to be far more sensitive than the BOLD technique in preclinical studies, it may potentially expand the role of fMRI in clinical applications. The CBF method provides more quantitative information than the BOLD signal, albeit at a significant loss of detection sensitivity.

Interventional MRI

The lack of harmful effects on the patient and the operator make MRI well-suited for "interventional radiology", where the images produced by a MRI scanner are used to guide minimally-invasive procedures. Of course, such procedures must be done without *any* ferromagnetic instruments.

A specialized growing subset of interventional MRI is that of intraoperative MRI in which the MRI is used in the surgical process. Some specialized MRI systems have been developed that allow imaging concurrent with the surgical procedure. More typical, however, is that the surgical procedure is temporarily interrupted so that MR images can be acquired to verify the success of the procedure or guide subsequent surgical work.

Radiation therapy simulation

Because of MRI's superior imaging of soft tissues, it is now being utilized to specifically locate tumors within the body in preparation for radiation therapy treatments. For therapy simulation, a patient is placed in specific, reproducible, body position and scanned. The MRI system then computes the precise location, shape and orientation of the tumor mass, correcting for any spatial distortion inherent in the system. The patient is then marked or tattooed with points which, when combined with the specific body position, will permit precise triangulation for radiation therapy.

Current density imaging

Current density imaging (CDI) endeavors to use the phase information from images to reconstruct current densities within a subject. Current density imaging works because electrical currents generate magnetic fields, which in turn affect the phase of the magnetic dipoles during an imaging sequence. To date no successful CDI has been performed using biological currents, but several studies have been published which involve currents applied through a pair of electrodes.

Magnetic resonance guided focused ultrasound

In MRgFUS therapy, ultrasound beams are focused on a tissue—guided and controlled using MR thermal imaging—and due to the significant energy deposition at the focus, temperature within the tissue rises to more than 65 °C (150 °F), completely destroying it. This technology can achieve precise "ablation" of diseased tissue. MR imaging provides a three-dimensional view of the target tissue, allowing for precise focusing of ultrasound energy. The MR imaging provides quantitative, real-time, thermal images of the treated area. This allows the physician to ensure that the temperature generated during each cycle of ultrasound energy is sufficient to cause thermal ablation within the desired tissue and if not, to adapt the parameters to ensure effective treatment.

Multinuclear imaging

Hydrogen is the most frequently imaged nucleus in MRI because it is present in biological tissues in great abundance. However, any nucleus which has a net nuclear spin could potentially be imaged with MRI. Such nuclei include helium-3, carbon-13, fluorine-19, oxygen-17, sodium-23, phosphorus-31 and xenon-129. ^{23}Na , ^{31}P and ^{17}O are naturally abundant in the body, so can be imaged directly. Gaseous isotopes such as ^3He or ^{129}Xe must be hyperpolarized and then inhaled as their nuclear density is too low to yield a useful signal under normal conditions. ^{17}O , ^{13}C and ^{19}F can be administered in sufficient quantities in liquid form (e.g. ^{17}O -water, ^{13}C -glucose solutions or perfluorocarbons) that hyperpolarization is not a necessity.

Multinuclear imaging is primarily a research technique at present. However, potential applications include functional imaging and imaging of organs poorly seen on ^1H MRI (e.g. lungs and bones) or as alternative contrast agents. Inhaled hyperpolarized ^3He can be used to image the distribution of air spaces within the lungs. Injectable solutions containing ^{13}C or stabilized bubbles of hyperpolarized ^{129}Xe have been studied as contrast agents for angiography and perfusion imaging. ^{31}P can potentially provide information on bone density and structure, as well as functional imaging of the brain.

Susceptibility weighted imaging (SWI)

Susceptibility weighted imaging (SWI), is a new type of contrast in MRI different from spin density, T_1 , or T_2 imaging. This method exploits the susceptibility differences between tissues and uses a fully velocity compensated, three dimensional, RF spoiled, high-resolution, 3D gradient echo scan. This special data acquisition and image processing produces an enhanced contrast magnitude image very sensitive to venous blood, hemorrhage and iron storage. It is used to enhance the detection and diagnosis of tumors, vascular and neurovascular diseases (stroke and hemorrhage, multiple sclerosis, Alzheimer's), and also detects traumatic brain injuries that may not be diagnosed using other methods.^{[18] [19]}

Other specialized MRI techniques

MRI is a new and active field of research and new methods and variants are often published when they are able to get better results in specific fields. Examples of these recent improvements are T_2^* -weighted turbo spin-echo (T_2 TSE MRI), double inversion recovery MRI (DIR-MRI) or phase-sensitive inversion recovery MRI (PSIR-MRI), all of them able to improve imaging of the brain lesions^{[20] [21]}. Another example is MP-RAGE (magnetization-prepared rapid acquisition with gradient echo)^[22], which improves images of multiple sclerosis cortical lesions^[23].

Portable instruments

Portable magnetic resonance instruments are available for use in education and field research. Using the principles of Earth's field NMR, they have no powerful polarizing magnet, so that such instruments can be small and inexpensive. Some can be used for both EFNMR spectroscopy and MRI imaging^[24]. The low strength of the Earth's field results in poor signal to noise ratios, requiring long scan times to capture spectroscopic data or build up MRI images.

Research with atomic magnetometers have discussed the possibility for cheap and portable MRI instruments without the large magnet.^{[25] [26]}

MRI versus CT

A computed tomography (CT) scanner uses X-rays, a type of ionizing radiation, to acquire its images, making it a good tool for examining tissue composed of elements of a higher atomic number than the tissue surrounding them, such as bone and calcifications (calcium based) within the body (carbon based flesh), or of structures (vessels, bowel). MRI, on the other hand, uses non-ionizing radio frequency (RF) signals to acquire its images and is best suited for non-calcified tissue, though MR images can also be acquired from bones and teeth^[27] as well as fossils.^[28]

CT may be enhanced by use of contrast agents containing elements of a higher atomic number than the surrounding flesh such as iodine or barium. Contrast agents for MRI are those which have paramagnetic properties, e.g. gadolinium and manganese.

Both CT and MRI scanners can generate multiple two-dimensional cross-sections (slices) of tissue and three-dimensional reconstructions. Unlike CT, which uses only X-ray attenuation to generate image contrast, MRI has a long list of properties that may be used to generate image contrast. By variation of scanning parameters, tissue contrast can be altered and enhanced in various ways to detect different features. (See Applications above.)

MRI can generate cross-sectional images in any plane (including oblique planes). In the past, CT was limited to acquiring images in the axial (or near axial) plane. The scans used to be called Computed *Axial* Tomography scans (CAT scans). However, the development of multi-detector CT scanners with near-isotropic resolution, allows the CT scanner to produce data that can be retrospectively reconstructed in any plane with minimal loss of image quality.

For purposes of tumor detection and identification in the brain, MRI is generally superior.^{[29] [30] [31]} However, in the case of solid tumors of the abdomen and chest, CT is often preferred due to less motion artifact. Furthermore, CT usually is more widely available, faster, less expensive, and may be less likely to require the person to be sedated or anesthetized.

MRI is also best suited for cases when a patient is to undergo the exam several times successively in the short term, because, unlike CT, it does not expose the patient to the hazards of ionizing radiation.

Economics of MRI

MRI equipment is expensive. 1.5 tesla scanners often cost between \$1 million and \$1.5 million USD. 3.0 tesla scanners often cost between \$2 million and \$2.3 million USD. Construction of MRI suites can cost up to \$500,000 USD, or more, depending on project scope.

MRI scanners have been significant sources of revenue for healthcare providers in the US. This is because of favorable reimbursement rates from insurers and federal government programs. Insurance reimbursement is provided in two components, an equipment charge for the actual performance of the MRI scan and professional charge for the radiologist's review of the images and/or data. In the US Northeast, an equipment charge might be \$3,500 and a professional charge might be \$350^[32] although the actual fees received by the equipment owner and interpreting physician are often quite less and depend on the rates negotiated with insurance companies or determined by governmental action as in the Medicare Fee Schedule. For example, an orthopedic surgery group in Illinois billed a charge of \$1,116 for a knee MRI in 2007 but the Medicare reimbursement in 2007 was only \$470.91^[33]. Many insurance companies require preapproval of an MRI procedure as a condition for coverage.

In the US, the 2007 Deficit Reduction Act (DRA) significantly reduced reimbursement rates paid by federal insurance programs for the equipment component of many scans, shifting the economic landscape. Many private insurers have followed suit.

Installation of the MRI unit



Heavy lifting equipment is used to install the MRI unit.

An MRI unit is a rather large item, typically requiring heavy equipment (such as cranes) to move the unit to its final location. Once the MRI unit is in place, the room that houses it is usually "built up" around the unit itself. See this page ^[34] for an example of the complexity involved in installing an MRI unit in a clinical setting. ^[35]

Safety

Death and injuries have occurred from projectiles created by the magnetic field, although few compared to the millions of examinations administered.^[36] ^[37] MRI makes use of powerful magnetic fields which, though they have not been demonstrated to cause direct biological damage, can interfere with metallic and electromechanical devices. Additional (small) risks are presented by the radio frequency systems, components or elements of the MRI system's operation, elements of the scanning procedure and medications that may be administered to facilitate MRI imaging.

Of great concern is the dramatic increase in the number of reported MRI accidents to the U.S. Food and Drug Administration (FDA). Since 2004, the last year in which a decline in the number of MRI accidents was reported, the full spectrum of MRI accidents has increased significantly in the following years. The 2008 FDA accident report data ^[38] culminates in a 277% increase over the 2004 rate.

There are many steps that the MRI patient and referring physician can take to help reduce the remaining risks, including providing a full, accurate and thorough medical history to the MRI provider.

Several of the specific MRI safety considerations are identified below:

Implants and foreign bodies

Pacemakers are generally considered an absolute contraindication towards MRI scanning, though highly specialized protocols have been developed to permit scanning of select pacing devices. Several cases of arrhythmia or death have been reported in patients with pacemakers who have undergone MRI scanning without appropriate precautions. Other electronic implants have varying contraindications, depending upon scanner technology, and implant properties, scanning protocols and anatomy being imaged.

Many other forms of medical or biostimulation implants may be contraindicated for MRI scans. These may include vagus nerve stimulators, implantable cardioverter-defibrillators, loop recorders, insulin pumps, cochlear implants, deep brain stimulators, and many others. Medical device patients should always present complete information (manufacturer, model, serial number and date of implantation) about all implants to both the referring physician and to the radiologist or technologist before entering the room for the MRI scan.

While these implants pose a current problem, scientists and manufacturers are working on improved designs which will further minimize the risks that MRI scans pose to medical device operations. One such development in the works is a nano-coating for implants intended to screen them from the radio frequency waves, helping to make MRI exams available to patients currently prohibited from receiving them. The current article ^[39] for this is from New Scientist.

Ferromagnetic foreign bodies (e.g. shell fragments), or metallic implants (e.g. surgical prostheses, aneurysm clips) are also potential risks, and safety aspects need to be considered on an individual basis. Interaction of the magnetic

and radio frequency fields with such objects can lead to trauma due to movement of the object in the magnetic field, thermal injury from radio-frequency induction heating of the object, or failure of an implanted device. These issues are especially problematic when dealing with the eye. Most MRI centers require an orbital x-ray to be performed on anyone suspected of having metal fragments in their eyes, something not uncommon in metalworking.

Because of its non-ferromagnetic nature and poor electrical conductivity, titanium and its alloys are useful for long term implants and surgical instruments intended for use in image-guided surgery. In particular, not only is titanium safe from movement from the magnetic field, but artifacts around the implant are less frequent and less severe than with more ferromagnetic materials e.g. stainless steel. Artifacts from metal frequently appear as regions of empty space around the implant—frequently called 'black-hole artifact'. E.g. a 3 mm titanium alloy coronary stent may appear as a 5 mm diameter region of empty space on MRI, whereas around a stainless steel stent, the artifact may extend for 10–20 mm or more.

In 2006, a new classification system for implants and ancillary clinical devices has been developed by ASTM International and is now the standard supported by the US Food and Drug Administration:

MR-Safe — The device or implant is completely non-magnetic, non-electrically conductive, and non-RF reactive, eliminating all of the primary potential threats during an MRI procedure.



MR Safe sign

MR-Conditional — A device or implant that may contain magnetic, electrically conductive or RF-reactive components that is safe for operations in proximity to the MRI, provided the conditions for safe operation are defined and observed (such as 'tested safe to 1.5 teslas' or 'safe in magnetic fields below 500 gauss in strength').



MR Conditional sign

MR-Unsafe — Nearly self-explanatory, this category is reserved for objects that are significantly ferromagnetic and pose a clear and direct threat to persons and equipment within the magnet room.

Though the current classification system was originally developed for regulatory-approved medical devices, it is being applied to all manner of items, appliances and equipment intended for use in the MR environment.

In the case of pacemakers, the risk is thought to be primarily RF induction in the pacing electrodes/wires causing inappropriate pacing of the heart, rather than the magnetic field affecting the pacemaker itself. Much research and development is being undertaken, and many tools are being developed in order to predict the effects of the RF fields inside the body.

Patients who have been prescribed MRI exams who are concerned about safety may be interested in the 10 Questions To Ask Your MRI Provider ^[40].

MRI providers who wish to measure the degree to which they have effectively addressed the safety issues for patients and staff may be interested in the MRI Suite Safety Calculator ^[41] provided through a radiology website.



Projectile or missile effect

As a result of the very high strength of the magnetic field needed to produce scans (frequently up to 60,000 times the Earth's own magnetic field effects), there are several incidental safety issues addressed in MRI facilities. Missile-effect accidents, where ferromagnetic objects are attracted to the center of the magnet, have resulted in injury and death.^[36] ^[37] A video simulation of a fatal projectile effect accident ^[42] illustrates the extreme power that contemporary MRI equipment can exert on ferromagnetic objects.

In order to help reduce the risks of projectile accidents, ferromagnetic objects and devices are typically prohibited in proximity to the MRI scanner, with non-ferromagnetic versions of many tools and devices typically retained by the scanning facility. Patients undergoing MRI examinations are required to remove all metallic objects, often by changing into a gown or scrubs.

New ferromagnetic-only detection devices are proving highly effective in supplementing conventional screening techniques in many leading hospitals and imaging centers and are now recommended by the American College of Radiology's *Guidance Document for Safe MR Practices: 2007* ^[43], the United States' Veterans Administration's Design Guide ^[44] and the Joint Commission's Sentinel Event Alert #38 ^[45].

The magnetic field and the associated risk of missile-effect accidents remains a permanent hazard — as superconductive MRI magnets retain their magnetic field, even in the event of a power outage.

Radio frequency energy

A powerful radio transmitter is needed for excitation of proton spins. This can heat the body to the point of risk of hyperthermia in patients, particularly in obese patients or those with thermoregulation disorders. Several countries have issued restrictions on the maximum specific absorption rate that a scanner may produce.

Peripheral nerve stimulation (PNS)

The rapid switching on and off of the magnetic field gradients is capable of causing nerve stimulation. Volunteers report a twitching sensation when exposed to rapidly switched fields, particularly in their extremities. The reason the peripheral nerves are stimulated is that the changing field increases with distance from the center of the gradient coils (which more or less coincides with the center of the magnet). Note however that when imaging the head, the

heart is far off-center and induction of even a tiny current into the heart must be avoided at all costs. Although PNS was not a problem for the slow, weak gradients used in the early days of MRI, the strong, rapidly switched gradients used in techniques such as EPI, fMRI, diffusion MRI, etc. are indeed capable of inducing PNS. American and European regulatory agencies insist that manufacturers stay below specified dB/dt limits (dB/dt is the change in field per unit time) or else prove that no PNS is induced for any imaging sequence. As a result of dB/dt limitation, commercial MRI systems cannot use the full rated power of their gradient amplifiers.

Acoustic noise

Switching of field gradients causes a change in the Lorentz force experienced by the gradient coils, producing minute expansions and contractions of the coil itself. As the switching is typically in the audible frequency range, the resulting vibration produces loud noises (clicking or beeping). This is most marked with high-field machines and rapid-imaging techniques in which sound intensity can reach 120 dB(A) (equivalent to a jet engine at take-off) ^[46].

Appropriate use of ear protection is essential for anyone inside the MRI scanner room during the examination. ^[47]

Cryogenics

As described above in #Scanner construction and operation, many MRI scanners rely on cryogenic liquids to enable superconducting capabilities of the electromagnetic coils within. Though the cryogenic liquids most frequently used are non-toxic, their physical properties present specific hazards.

An emergency shut-down of a superconducting electromagnet, an operation known as "quenching", involves the rapid boiling of liquid helium from the device. If the rapidly expanding helium cannot be dissipated through an external vent, sometimes referred to as 'quench pipe', it may be released into the scanner room where it may cause displacement of the oxygen and present a risk of asphyxiation. ^[48]

Liquid helium, the most commonly used cryogen in MRI, undergoes near explosive expansion as it changes from liquid to a gaseous state. Rooms built in support of superconducting MRI equipment should be equipped with pressure relief mechanisms ^[49] and an exhaust fan, in addition to the required quench pipe.

Since a quench results in rapid loss of all cryogenics in the magnet, recommissioning the magnet is extremely expensive and time-consuming. Spontaneous quenches are uncommon, but may also be triggered by equipment malfunction, improper cryogen fill technique, contaminants inside the cryostat, or extreme magnetic or vibrational disturbances.

Contrast agents

The most commonly used intravenous contrast agents are based on chelates of gadolinium. In general, these agents have proved safer than the iodinated contrast agents used in X-ray radiography or CT. Anaphylactoid reactions are rare, occurring in approx. 0.03–0.1%. ^[50] Of particular interest is the lower incidence of nephrotoxicity, compared with iodinated agents, when given at usual doses—this has made contrast-enhanced MRI scanning an option for patients with renal impairment, who would otherwise not be able to undergo contrast-enhanced CT. ^[51]

Although gadolinium agents have proved useful for patients with renal impairment, in patients with severe renal failure requiring dialysis there is a risk of a rare but serious illness, nephrogenic systemic fibrosis, that may be linked to the use of certain gadolinium-containing agents. The most frequently linked is gadodiamide, but other agents have been linked too. ^[52] Although a causal link has not been definitively established, current guidelines in the United States are that dialysis patients should only receive gadolinium agents where essential, and that dialysis should be performed as soon as possible after the scan is complete, in order to remove the agent from the body promptly. ^[53] In Europe, where more gadolinium-containing agents are available, a classification of agents according to potential risks has been released. ^[54] ^[55] Recently a new contrast agent named gadoxetate, brand name Eovist (US) or Primovist (EU), was approved for diagnostic use: this has the theoretical benefit of a dual excretion path. ^[56]

Pregnancy

No effects of MRI on the fetus have been demonstrated.^[57] In particular, MRI avoids the use of ionizing radiation, to which the fetus is particularly sensitive. However, as a precaution, current guidelines recommend that pregnant women undergo MRI only when essential. This is particularly the case during the first trimester of pregnancy, as organogenesis takes place during this period. The concerns in pregnancy are the same as for MRI in general, but the fetus may be more sensitive to the effects—particularly to heating and to noise. However, one additional concern is the use of contrast agents; gadolinium compounds are known to cross the placenta and enter the fetal bloodstream, and it is recommended that their use be avoided.

Despite these concerns, MRI is rapidly growing in importance as a way of diagnosing and monitoring congenital defects of the fetus because it can provide more diagnostic information than ultrasound and it lacks the ionizing radiation of CT. MRI without contrast agents is the imaging mode of choice for pre-surgical, in-utero diagnosis and evaluation of fetal tumors, primarily teratomas, facilitating open fetal surgery, other fetal interventions, and planning for procedures (such as the EXIT procedure) to safely deliver and treat babies whose defects would otherwise be fatal.

Claustrophobia and discomfort

Due to the construction of some MRI scanners, they can be potentially unpleasant to lie in. Older models of closed bore MRI systems feature a fairly long tube or tunnel. The part of the body being imaged needs to lie at the center of the magnet which is at the absolute center of the tunnel. Because scan times on these older scanners may be long (occasionally up to 40 minutes for the entire procedure), people with even mild claustrophobia are sometimes unable to tolerate an MRI scan without management. Modern scanners may have larger bores (up to 70 cm) and scan times are shorter. This means that claustrophobia is less of an issue, and many patients now find MRI an innocuous and easily tolerated procedure.

Nervous patients may still find the following strategies helpful:

- Advance preparation
 - visiting the scanner to see the room and practice lying on the table
 - visualization techniques
 - chemical sedation
 - general anesthesia
- Coping while inside the scanner
 - holding a "panic button"
 - closing eyes as well as covering them (e.g. washcloth, eye mask)
 - listening to music on headphones or watching a movie with a Head-mounted display while in the machine
 - Scan Rooms with lighting, sound and images on the wall. Some rooms come with images on the walls or ceiling.

Alternative scanner designs, such as open or upright systems, can also be helpful where these are available. Though open scanners have increased in popularity, they produce inferior scan quality because they operate at lower magnetic fields than closed scanners. However, commercial 1.5 tesla open systems have recently become available, providing much better image quality than previous lower field strength open models^[58].

For babies and young children chemical sedation or general anesthesia are the norm, as these subjects cannot be instructed to hold still during the scanning session. Obese patients and pregnant women may find the MRI machine to be a tight fit. Pregnant women may also have difficulty lying on their backs for an hour or more without moving.

Acoustic noise associated with the operation of an MRI scanner can also exacerbate the discomfort associated with the procedure.

Guidance

Safety issues, including the potential for biostimulation device interference, movement of ferromagnetic bodies, and incidental localized heating, have been addressed in the American College of Radiology's *White Paper on MR Safety* which was originally published in 2002 and expanded in 2004. The *ACR White Paper on MR Safety* has been rewritten and was released early in 2007 under the new title *ACR Guidance Document for Safe MR Practices* ^[43].

In December 2007, the Medicines in Healthcare product Regulation Agency (MHRA), a UK healthcare regulatory body, issued their *Safety Guidelines for Magnetic Resonance Imaging Equipment in Clinical Use* ^[59].

In February 2008, the Joint Commission, a US healthcare accrediting organization, issued a Sentinel Event Alert #38 ^[45], their highest patient safety advisory, on MRI safety issues.

In July 2008, the United States Veterans Administration, a federal governmental agency serving the healthcare needs of former military personnel, issued a substantial revision to their *MRI Design Guide* ^[60] which includes physical or facility safety considerations.

The European Physical Agents Directive

The European Physical Agents (Electromagnetic Fields) Directive is legislation adopted in European legislature. Originally scheduled to be required by the end of 2008, each individual state within the European Union must include this directive in its own law by the end of 2012. Some member nations passed complying legislation and are now attempting to repeal their state laws in expectation that the final version of the EU Physical Agents Directive will be substantially revised prior to the revised adoption date.

The directive applies to occupational exposure to electromagnetic fields (not medical exposure) and was intended to limit workers' acute exposure to strong electromagnetic fields, as may be found near electricity substations, radio or television transmitters or industrial equipment. However, the regulations impact significantly on MRI, with separate sections of the regulations limiting exposure to static magnetic fields, changing magnetic fields and radio frequency energy. Field strength limits are given which may not be exceeded for any period of time. An employer may commit a criminal offense by allowing a worker to exceed an exposure limit if that is how the Directive is implemented in a particular Member State.

The Directive is based on the international consensus of established effects of exposure to electromagnetic fields, and in particular the advice of the European Commissions's advisor, the International Commission on Non-Ionizing Radiation Protection (ICNIRP). The aims of the Directive, and the ICNIRP guidelines upon which it is based, are to prevent exposure to potentially harmful fields. The actual limits in the Directive are very similar to the limits advised by the Institute of Electrical and Electronics Engineers, with the exception of the frequencies produced by the gradient coils, where the IEEE limits are significantly higher.

Many Member States of the EU already have either specific EMF regulations or (as in the UK) a general requirement under workplace health and safety legislation to protect workers against electromagnetic fields. In almost all cases the existing regulations are aligned with the ICNIRP limits so that the Directive should, in theory, have little impact on any employer already meeting their legal responsibilities.

The introduction of the Directive has brought to light an existing potential issue with occupational exposures to MRI fields. There are at present very few data on the number or types of MRI practice that might lead to exposures in excess of the levels of the Directive. ^[61] ^[62] There is a justifiable concern amongst MRI practitioners that if the Directive were to be enforced more vigorously than existing legislation, the use of MRI might be restricted, or working practices of MRI personnel might have to change.

In the initial draft a limit of static field strength to 2 T was given. This has since been removed from the regulations, and whilst it is unlikely to be restored as it was without a strong justification, some restriction on static fields may be reintroduced after the matter has been considered more fully by ICNIRP. The effect of such a limit might be to restrict the installation, operation and maintenance of MRI scanners with magnets of 2 T and stronger. As the increase in field strength has been instrumental in developing higher resolution and higher performance scanners,

this would be a significant step back. This is why it is unlikely to happen without strong justification.

Individual government agencies and the European Commission have now formed a working group to examine the implications on MRI and to try to address the issue of occupational exposures to electromagnetic fields from MRI.

Three-dimensional (3D) image reconstruction

The principle

Because contemporary MRI scanners offer isotropic, or near isotropic, resolution, display of images does not need to be restricted to the conventional axial images. Instead, it is possible for a software program to build a volume by 'stacking' the individual slices one on top of the other. The program may then display the volume in an alternative manner.

3D rendering techniques

Surface rendering

A threshold value of greyscale density is chosen by the operator (e.g. a level that corresponds to fat). A threshold level is set, using edge detection image processing algorithms. From this, a 3-dimensional model can be constructed and displayed on screen. Multiple models can be constructed from various different thresholds, allowing different colors to represent each anatomical component such as bone, muscle, and cartilage. However, the interior structure of each element is not visible in this mode of operation.

Volume rendering

Surface rendering is limited in that it will only display surfaces which meet a threshold density, and will only display the surface that is closest to the imaginary viewer. In volume rendering, transparency and colors are used to allow a better representation of the volume to be shown in a single image - e.g. the bones of the pelvis could be displayed as semi-transparent, so that even at an oblique angle, one part of the image does not conceal another.

Image segmentation

Where different structures have similar threshold density, it can become impossible to separate them simply by adjusting volume rendering parameters. The solution is called segmentation, a manual or automatic procedure that can remove the unwanted structures from the image.

2003 Nobel Prize

Reflecting the fundamental importance and applicability of MRI in the medical field, Paul Lauterbur of the University of Illinois at Urbana-Champaign and Sir Peter Mansfield of the University of Nottingham were awarded the 2003 Nobel Prize in Physiology or Medicine for their "discoveries concerning magnetic resonance imaging". The Nobel Prize committee acknowledged Lauterbur's insight of using magnetic field gradients to introduce spatial localization, a discovery that allowed rapid acquisition of 2D images. Mansfield was credited with introducing the mathematical formalism and developing techniques for efficient gradient utilization and fast imaging. The actual research for which the prize was awarded was done almost 30 years ago, while Paul Lauterbur was at Stony Brook University in New York.

The award was vigorously protested by Raymond Vahan Damadian, founder of FONAR Corporation, who claimed that he was the inventor of MRI,^[3] and that Lauterbur and Mansfield had merely refined the technology.^[63] An ad hoc group, called "The Friends of Raymond Damadian", took out full-page advertisements in the *New York Times* and *The Washington Post* entitled "The Shameful Wrong That Must Be Righted", demanding that he be awarded at least a share of the Nobel Prize.^[64] Also, even earlier, in the Soviet Union, Vladislav Ivanov filed (in 1960) a

document with the USSR State Committee for Inventions and Discovery at Leningrad for a Magnetic Resonance Imaging device^[65], although this was not approved until the 1970s.^[66] In a letter to *Physics Today*, Herman Carr pointed out his own even earlier use of field gradients for one-dimensional MR imaging.^[67]

See also

- Earth's field NMR (EFNMR)
- Electron-spin resonance (spin physics)
- History of brain imaging
- Medical imaging
- Magnetic immunoassay
- Jemris (open source MRI simulator)
- *Magnetic Resonance Imaging (journal)*
- Magnetic resonance microscopy
- Magnetic Particle Imaging (MPI)
- Magnetic resonance elastography
- Neuroimaging software
- Nephrogenic fibrosing dermopathy
- Nobel Prize controversies
- Nuclear magnetic resonance (NMR)
- 2D-FT NMRI and Spectroscopy
- Relaxation
- Robinson oscillator
- Rabi cycle
- Virtopsy

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External links

- Listing of MRI Types^[68] - All Inclusive Listing of MRI Types
- www.mri-tutorial.com^[69] - MRI-TUTORIAL.COM | A free learning repository about neuroimaging
- mri.startkabel.nl^[70] - Grote verzameling MRI-gerelateerde links
- BIGS-animation^[71] - Physics of MRI like spin, modification of spin or pulse sequences
- MDCT^[72] - Free Radiology Resource For Radiographers, Radiologists and Technical Assistants
- A Guided Tour of MRI: An introduction for laypeople^[73] National High Magnetic Field Laboratory
- Joseph P. Hornak, Ph.D. The Basics of MRI^[74]. *Underlying physics and technical aspects*.
- Video: What to Expect During Your MRI Exam^[75] from the Institute for Magnetic Resonance Safety, Education, and Research (IMRSE)
- Interactive Flash Animation on MRI^[76] - *Online Magnetic Resonance Imaging physics and technique course*
- International Society for Magnetic Resonance in Medicine^[17]
- Article on helium scarcity and potential effects on NMR and MRI communities^[77]
- Danger of objects flying into the scanner^[18]
- Video compiled of MRI scans showing arachnoid cyst^[78]
- JEMRIS^[79] - Parallel and single-core general MRI Simulator
- Professor Laurance Hall^[80] - Daily Telegraph obituary
- mri-physics.com^[81] - Online MRI physics textbook.

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